NITROSATED GLUTAMIC ACID COMPOUNDS, COMPOSITIONS AND METHODS OF USE

Related Applications

This application claims priority under 35 USC § 119 to US Application No. 60/505,921 filed September 26, 2003.

Field of the Invention

The invention describes novel nitrosated glutamic acid compounds and pharmaceutically acceptable salts thereof, and novel compositions comprising at least one nitrosated glutamic acid compound, and, optionally, at least one nitric oxide donor and/or at least one therapeutic agent. The invention also provides novel kits comprising at least one nitrosated glutamic acid compound, and, and, optionally, at least one nitric oxide donor compound and/or at least one therapeutic agent. The invention also provides methods for (a) treating cardiovascular diseases; (b) treating renovascular diseases; (c) treating diabetes; (d) treating diseases resulting from oxidative stress; (e) treating endothelial dysfunctions; (f) treating diseases caused by endothelial dysfunctions; (g) treating cirrhosis; (h) treating pre-eclampsia; (j) treating osteoporosis; (k) treating nephropathy; (l) treating diseases resulting from elevated levels of gamma-glutamyl transpeptidase and (m) the targeted delivery of compounds and nitric oxide to organs, cells or tissues containing the enzyme gamma-glutamyl transpeptidase.

Background of the Invention

The chemical modification of a biologically active compound to give a new chemical from which the active compound can be generated by enzymatic action is an important strategy to target drug action to specific cells and tissues and thereby decrease toxicity or side effects on non-target cells. The enzyme, gamma-glutamyl transpeptidase, is present in various biological tissues, such as kidney, prostate, pancreas as well as in urine and blood serum. In addition, elevated levels of gamma-glutamyl transpeptidase activity in serum is an indication of liver diseases, and extremely high levels have been associated with cancer of the liver, bile duct obstructions, and myocardial infarction. Thus the targeted delivery of compounds to organs, cells and tissues containing the enzyme gamma-glutamyl transpeptidase is an effective means of delivering the active compound at the required site of action and can

result in biologically active compounds with improved efficacy, lower toxicity and that can be used at low dosages. The invention is directed to these, as well as other, important ends.

Summary of the Invention

The invention provides novel glutamic acid compounds and derivatives thereof that are substituted with at least one NO_2 group (i.e., nitrosated), and pharmaceutically acceptable salts thereof. The glutamic acid compound can be nitrosated through one or more sites such as oxygen (hydroxyl condensation), sulfur (sulfhydryl condensation) and/or nitrogen. The invention also provides compositions comprising the novel compounds described herein in a pharmaceutically acceptable carrier.

The invention is also based on the discovery that administering at least one glutamic acid compound or pharmaceutically acceptable salts thereof, that is substituted with at least one NO_2 group (i.e., nitrosated glutamic acid compound), and, optionally, at least one nitric oxide donor can be used for the targeted delivery of the compounds to organs, cells or tissues containing the enzyme gamma-glutamyl transpeptidase and for the delivery of nitric oxide at the targeted site. Nitric oxide donors include, for example, S-nitrosothiols, nitrites, nitrates, N-oxo-N-nitrosamines, SPM 3672, SPM 5185, SPM 5186 and analogues thereof, and substrates of the various isozymes of nitric oxide synthase. Thus, another embodiment of the invention provides compositions comprising at least one glutamic acid compound that is substituted with at least one NO_2 group (i.e., nitrosated), and at least one nitric oxide donor compound. The invention also provides for such compositions in a pharmaceutically acceptable carrier.

The invention provides compositions comprising at least one nitrosated glutamic acid compound, and, optionally, at least one nitric oxide donor compound and/or at least one therapeutic agent, including, but not limited to, aldosterone antagonists, alpha-adrenergic receptor antagonists, angiotensin II antagonists, angiotensin-converting enzyme (ACE) inhibitors, antidiabetic compounds, anti-hyperlipidemic compounds, antioxidants, antithrombotic and vasodilator compounds, β-adrenergic antagonists, calcium channel blockers, digitalis, diuretics, endothelin antagonists, hydralazine compounds, H_2 receptor antagonists, neutral endopeptidase inhibitors, nonsteroidal antiinflammatory compounds (NSAIDs), phosphodiesterase

inhibitors, potassium channel blockers, platelet reducing agents, proton pump inhibitors, renin inhibitors, selective cyclooxygenase-2 (COX-2) inhibitors, and combinations of two or more thereof. In a preferred embodiment the at least one therapeutic agent is selected from the group consisting of an aldosterone antagonist, an angiotensin II antagonist, an angiotensin-converting enzyme (ACE) inhibitors, a β-adrenergic antagonist, a digitalis, a diuretic, and a hydralazine compound. The invention also provides for such compositions in a pharmaceutically acceptable carrier.

The invention provides methods for (a) treating cardiovascular diseases; (b) treating renovascular diseases; (c) treating diabetes; (d) treating diseases resulting from oxidative stress; (e) treating endothelial dysfunctions; (f) treating diseases caused by endothelial dysfunctions; (g) treating cirrhosis; (h) treating pre-eclampsia; (j) treating osteoporosis; (k) treating nephropathy; (l) treating diseases resulting from elevated levels of gamma-glutamyl transpeptidase and (m) the targeted delivery of compounds and nitric oxide to organs, cells or tissues containing the enzyme gamma-glutamyl transpeptidase in a patient in need thereof comprising administering to the patient a therapeutically effective amount of at least one nitrosated glutamic acid compound, and, optionally, at least one therapeutic agent, such as, for example, aldosterone antagonists, alpha-adrenergic receptor antagonists, angiotensin II antagonists, angiotensin-converting enzyme (ACE) inhibitors, antidiabetic compounds, anti-hyperlipidemic compounds, antioxidants, antithrombotic and vasodilator compounds, β-adrenergic antagonists, calcium channel blockers, digitalis, diuretics, endothelin antagonists, hydralazine compounds, H_2 receptor antagonists, neutral endopeptidase inhibitors, nonsteroidal antiinflammatory compounds (NSAIDs), phosphodiesterase inhibitors, potassium channel blockers, platelet reducing agents, proton pump inhibitors, renin inhibitors, selective cyclooxygenase-2 (COX-2) inhibitors, and combinations of two or more thereof. The methods can optionally further comprise the administration of at least one nitric oxide donor compound. In this embodiment of the invention, the methods can involve (i) administering the nitrosated glutamic acid compounds, (ii) administering the nitrosated glutamic acid compounds and therapeutic agents, or (iii) administering the nitrosated glutamic acid compounds, NO donors, and therapeutic agents. In a preferred embodiment the at least one therapeutic agent is selected from the

group consisting of an aldosterone antagonist, an angiotensin II antagonist, an angiotensin-converting enzyme (ACE) inhibitor, a β-adrenergic antagonist, a diuretic, and a hydralazine compound. The nitrosated glutamic acid compounds, nitric oxide donors, and/or therapeutic agents can be administered separately or as components of the same composition in one or more pharmaceutically acceptable carriers.

Another embodiment of the invention provides kits comprising at least one nitrosated glutamic acid compound, and, optionally, at least one nitric oxide donor compound. The kit can further comprise at least one therapeutic agent, such as, for example, aldosterone antagonists, alpha-adrenergic receptor antagonists, angiotensin II antagonists, angiotensin-converting enzyme (ACE) inhibitors, antidiabetic compounds, anti-hyperlipidemic compounds, antioxidants, antithrombotic and vasodilator compounds, β-adrenergic antagonists, calcium channel blockers, digitalis, diuretics, endothelin antagonists, hydralazine compounds, H_2 receptor antagonists, neutral endopeptidase inhibitors, nonsteroidal antiinflammatory compounds (NSAIDs), phosphodiesterase inhibitors, potassium channel blockers, platelet reducing agents, proton pump inhibitors, renin inhibitors, selective cyclooxygenase-2 (COX-2) inhibitors, and combinations of two or more thereof. The nitrosated glutamic acid compound, the nitric oxide donor and/or therapeutic agent, can be separate components in the kit or can be in the form of a composition in one or more pharmaceutically acceptable carriers.

These and other aspects of the invention are described in detail herein.

Detailed Description of the Invention

As used throughout the disclosure, the following terms, unless otherwise indicated, shall be understood to have the following meanings.

"Glutamic acid compound" refers to and includes derivatives of glutamic acid in which one of the hydrogen atoms of the peptide amino group is a lower alkyl group, such as, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, pentyl, neopentyl, iso-amyl, hexyl, octyl, and the like.

"Gamma-glutamyl transpeptidase" refers to an enzyme capable of hydrolyzing a gamma-glutamylpeptide and/or transferring the gamma-glutamyl radical to other peptides, amino acids, or the like.

"Cardiovascular disease or disorder" refers to any cardiovascular disease or disorder known in the art, including, but not limited to, congestive heart failure, restenosis, hypertension (e.g. pulmonary hypertension, labile hypertension, idiopathic hypertension, low-renin hypertension, salt-sensitive hypertension, low-renin, salt-sensitive hypertension, thromboembolic pulmonary hypertension; pregnancy-induced hypertension; renovascular hypertension; hypertension-dependent end-stage renal disease, hypertension associated with cardiovascular surgical procedures, hypertension with left ventricular hypertrophy, and the like), diastolic dysfunction, coronary artery disease, myocardial infarctions, cerebral infarctions, atherosclerosis, atherogenesis, cerebrovascular disease, angina, (including chronic, stable, unstable and variant (Prinzmetal) angina pectoris), aneurysm, ischemic heart disease, cerebral ischemia, myocardial ischemia, thrombosis, platelet aggregation, platelet adhesion, smooth muscle cell proliferation, vascular or non-vascular complications associated with the use of medical devices, wounds associated with the use of medical devices, vascular or non-vascular wall damage, peripheral vascular disease, neointimal hyperplasia following percutaneous transluminal coronary angiograph, vascular grafting, coronary artery bypass surgery, thromboembolic events, post-angioplasty restenosis, coronary plaque inflammation, hypercholesterolemia, embolism, stroke, shock, arrhythmia, atrial fibrillation or atrial flutter, thrombotic occlusion and reclusion cerebrovascular incidents, and the like

"Thromboembolic events" include, but are not limited to, ischemic stroke, transient ischemic stroke, myocardial infarction, angina pectoris, thrombosis (for example, restenosis, arterial thrombosis, coronary thrombosis, heart valve thrombosis, coronary stenosis, stent thrombosis, graft thrombosis, and first and subsequent thrombotic stroke, and the like), thromboembolism (for example, pulmonary thromboembolism, cerebral thromboembolism, and the like), thrombophlebitis, thrombocytopenia, bleeding disorders, thrombotic occlusion and reocclusion and acute vascular events. Patients who are at risk of developing thromboembolic events, may include those with a familial history of, or genetically predisposed to, thromboembolic disorders, who have had ischemic stroke, transient ischemic stroke, myocardial infarction, and those with unstable angina pectoris or chronic stable angina pectoris and

patients with altered prostacyclin/thromboxane A_2 homeostasis or higher than normal thromboxane A_2 levels leading to increase risk for thromboembolism, including patients with diabetes and rheumatoid arthritis.

"Diseases resulting from oxidative stress" refers to any disease that involves the generation of free radicals or radical compounds, such as, for example, atherogenesis, atheromatosis, arteriosclerosis, atherosclerosis, vascular hypertrophy associated with hypertension, hyperlipoproteinaemia, normal vascular degeneration through aging, parathyroidal reactive hyperplasia, renal disease (e.g., acute or chronic), neoplastic diseases, inflammatory diseases, neurological and acute bronchopulmonary disease, tumorigenesis, ischemia-reperfusion syndrome, arthritis, sepsis, cognitive dysfunction, endotoxic shock, endotoxin-induced organ failure, and the like.

"Renovascular diseases" refers to any disease or dysfunction of the renal system including, but not limited to, renal failure (e.g., acute or chronic), renal insufficiency, nephrotic edema, acute glomerulonephritis, oliguric renal failure, renal deterioration associated with severe hypertension, unilateral perechymal renal disease, polycystic kidney disease, chronic pyelonephritis, renal diseases associated with renal insufficiency, complications associated with dialysis or renal transplantation, renovascular hypertension, nephropathy, glomerulonephritis, scleroderma, glomerular sclerosis, and the like

"Endothelial dysfunction" refers to the impaired ability of any physiological process carried out by the endothelium, in particular, production of nitric oxide regardless of cause. It may be evaluated by, such as, for example, invasive techniques, such as, for example, coronary artery reactivity to acetylcholine or methacholine, and the like, or by noninvasive techniques, such as, for example, blood flow measurements, brachial artery flow dilation using cuff occlusion of the arm above or below the elbow, brachial artery ultrasonography, imaging techniques, measurement of circulating biomarkers, such as, asymmetric dimethylarginine (ADMA), and the like. For the latter measurement the endothelial-dependent flow-mediated dialation will be lower in patients diagnosed with an endothelial dysfunction.

"Methods for treating endothelial dysfunction" include, but are not limited to, treatment prior to the onset/diagnosis of a disease that is caused by or could result from

endothelial dysfunction, such as, for example, atherosclerosis, hypertension, diabetes, congestive heart failure, and the like.

"Methods for treating diseases caused by endothelial dysfunction" include, but are not limited to, the treatment of any disease resulting from the dysfunction of the endothelium, such as, for example, arteriosclerosis, congestive heart failure, hypertension, cardiovascular diseases, cerebrovascular diseases, renovascular diseases, mesenteric vascular diseases, pulmonary vascular diseases, ocular vascular diseases, peripheral vascular diseases, peripheral ischemic diseases, and the like.

"Therapeutic agent" includes any therapeutic agent that can be used to treat or prevent the diseases described herein. "Therapeutic agents" include, for example, aldosterone antagonists, alpha-adrenergic receptor antagonists, angiotensin II antagonists, angiotensin-converting enzyme (ACE) inhibitors, antidiabetic compounds, anti-hyperlipidemic compounds, antioxidants, antithrombotic and vasodilator compounds, β-adrenergic antagonists, calcium channel blockers, digitalis, diuretics, endothelin antagonists, hydralazine compounds, H_2 receptor antagonists, neutral endopeptidase inhibitors, nonsteroidal antiinflammatory compounds (NSAIDs), phosphodiesterase inhibitors, potassium channel blockers, platelet reducing agents, proton pump inhibitors, renin inhibitors, selective cyclooxygenase-2 (COX-2) inhibitors, and the like. Therapeutic agent includes the pharmaceutically acceptable salts thereof, pro-drugs, and pharmaceutical derivatives thereof including, but not limited to, the corresponding nitrosated and/or nitrosylated derivatives. Although nitric oxide donors have therapeutic activity, the term "therapeutic agent" does not include the nitric oxide donors described herein, since nitric oxide donors are separately defined.

"Prodrug" refers to a compound that is made more active *in vivo*.

"Antioxidant" refers to and includes any compound that can react and quench a free radical.

"Angiotensin converting enzyme (ACE) inhibitor" refers to compounds that inhibit an enzyme which catalyzes the conversion of angiotensin I to angiotensin II. ACE inhibitors include, but are not limited to, amino acids and derivatives thereof, peptides, including di- and tri-peptides, and antibodies to ACE which intervene in the

renin-angiotensin system by inhibiting the activity of ACE thereby reducing or eliminating the formation of the pressor substance angiotensin II.

"Angiotensin II antagonists" refers to compounds which interfere with the function, synthesis or catabolism of angiotensin II. Angiotensin II antagonists include peptide compounds and non-peptide compounds, including, but not limited to, angiotensin II antagonists, angiotensin II receptor antagonists, agents that activate the catabolism of angiotensin II, and agents that prevent the synthesis of angiotensin I from angiotensin II. The renin-angiotensin system is involved in the regulation of hemodynamics and water and electrolyte balance. Factors that lower blood volume, renal perfusion pressure, or the concentration of sodium in plasma tend to activate the system, while factors that increase these parameters tend to suppress its function.

"Anti-hyperlipidemic compounds" refers to any compound or agent that has the effect of beneficially modifying serum cholesterol levels such as, for example, lowering serum low density lipoprotein (LDL) cholesterol levels, or inhibiting oxidation of LDL cholesterol, whereas high density lipoprotein (HDL) serum cholesterol levels may be lowered, remain the same, or be increased. Preferably, the anti-hyperlipidemic compound brings the serum levels of LDL cholesterol and HDL cholesterol (and, more preferably, triglyceride levels) to normal or nearly normal levels.

"Diuretic compound" refers to and includes any compound or agent that increases the amount of urine excreted by a patient.

"Neutral endopeptidase inhibitors" refers to and includes compounds that are antagonists of the renin angiotensin aldosterone system including compounds that are dual inhibitors of neutral endopeptidases and angiotensin converting (ACE) enzymes.

"Renin inhibitors" refers to compounds which interfere with the activity of renin.

"Phosphodiesterase inhibitor" or "PDE inhibitor" refers to any compound that inhibits the enzyme phosphodiesterase. The term refers to selective or non-selective inhibitors of cyclic guanosine 3',5'-monophosphate phosphodiesterases (cGMP-PDE) and cyclic adenosine 3',5'-monophosphate phosphodiesterases (cAMP-PDE).

"Platelet reducing agents" refers to compounds that prevent the formation of a blood thrombus via any number of potential mechanisms. Platelet reducing agents

include, but are not limited to, fibrinolytic agents, anti-coagulant agents and any inhibitors of platelet function. Inhibitors of platelet function include agents that impair the ability of mature platelets to perform their normal physiological roles (i.e., their normal function, such as, for example, adhesion to cellular and non-cellular entities, aggregation, release of factors such as growth factors) and the like.

"Proton pump inhibitor" refers to any compound that reversibly or irreversibly blocks gastric acid secretion by inhibiting the H^+/K^+-ATP ase enzyme system at the secretory surface of the gastric parietal cell.

"NSAID" refers to a nonsteroidal anti-inflammatory compound or a nonsteroidal anti-inflammatory drug. NSAIDs inhibit cyclooxygenase, the enzyme responsible for the biosyntheses of the prostaglandins and certain autocoid inhibitors, including inhibitors of the various isozymes of cyclooxygenase (including but not limited to cyclooxygenase-1 and -2), and as inhibitors of both cyclooxygenase and lipoxygenase.

"Cyclooxygenase-2 (COX-2) selective inhibitor" refers to a compound that selectively inhibits the cyclooxygenase-2 enzyme over the cyclooxygenase-1 enzyme. In one embodiment, the compound has a cyclooxygenase-2 IC_{50} of less than about 2 μM and a cyclooxygenase-1 IC_{50} of greater than about 5 μM, in the human whole blood COX-2 assay (as described in Brideau et al., *Inflamm Res.*, 45: 68-74 (1996)) and also has a selectivity ratio of cyclooxygenase-2 inhibition over cyclooxygenase-1 inhibition of at least 10, and preferably of at least 40. In another embodiment, the compound has a cyclooxygenase-1 IC_{50} of greater than about 1 μM, and preferably of greater than 20 μM. The compound can also inhibit the enzyme, lipoxygenase. Such selectivity may indicate an ability to reduce the incidence of common NSAID-induced side effects.

"Patient" refers to animals, preferably mammals, most preferably humans, and includes males and females, and children and adults.

"Therapeutically effective amount" refers to the amount of the compound and/or composition that is effective to achieve its intended purpose.

"Transdermal" refers to the delivery of a compound by passage through the skin and into the blood stream.

"Transmucosal" refers to delivery of a compound by passage of the compound through the mucosal tissue and into the blood stream.

"Penetration enhancement" or "permeation enhancement" refers to an increase in the permeability of the skin or mucosal tissue to a selected pharmacologically active compound such that the rate at which the compound permeates through the skin or mucosal tissue is increased.

"Carriers" or "vehicles" refers to carrier materials suitable for compound administration and include any such material known in the art such as, for example, any liquid, gel, solvent, liquid diluent, solubilizer, or the like, which is non-toxic and which does not interact with any components of the composition in a deleterious manner.

"Sustained release" refers to the release of a therapeutically active compound and/or composition such that the blood levels of the therapeutically active compound are maintained within a desirable therapeutic range over a period of time. The sustained release formulation can be prepared using any conventional method known to one skilled in the art to obtain the desired release characteristics.

"Nitric oxide adduct" or "NO adduct" refers to compounds and functional groups which, under physiological conditions, can donate, release and/or directly or indirectly transfer any of the three redox forms of nitrogen monoxide (NO^+, NO^-, NO•), such that the biological activity of the nitrogen monoxide species is expressed at the intended site of action.

"Nitric oxide releasing" or "nitric oxide donating" refers to methods of donating, releasing and/or directly or indirectly transferring any of the three redox forms of nitrogen monoxide (NO^+, NO^-, NO•), such that the biological activity of the nitrogen monoxide species is expressed at the intended site of action.

"Nitric oxide donor" or "NO donor" refers to compounds that donate, release and/or directly or indirectly transfer a nitrogen monoxide species, and/or stimulate the endogenous production of nitric oxide or endothelium-derived relaxing factor (EDRF) *in vivo* and/or elevate endogenous levels of nitric oxide or EDRF *in vivo* and/or are oxidized to produce nitric oxide and/or are substrates for nitric oxide synthase and/or cytochrome P450. "NO donor" also includes compounds that are precursors of L-arginine, inhibitors of the enzyme arginase and nitric oxide mediators.

"Alkyl" refers to a lower alkyl group, a substituted lower alkyl group, a haloalkyl group, a hydroxyalkyl group, an alkenyl group, a substituted alkenyl group, an

alkynyl group, a bridged cycloalkyl group, a cycloalkyl group or a heterocyclic ring, as defined herein. An alkyl group may also comprise one or more radical species, such as, for example a cycloalkylalkyl group or a heterocyclicalkyl group.

"Lower alkyl" refers to branched or straight chain acyclic alkyl group comprising one to about ten carbon atoms (preferably one to about eight carbon atoms, more preferably one to about six carbon atoms). Exemplary lower alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, pentyl, neopentyl, iso-amyl, hexyl, octyl, and the like.

"Substituted lower alkyl" refers to a lower alkyl group, as defined herein, wherein one or more of the hydrogen atoms have been replaced with one or more R^{100} groups, wherein each R^{100} is independently a hydroxy, an ester, an amidyl, an oxo, a carboxyl, a carboxamido, a halo, a cyano, a nitrate or an amino group, as defined herein.

"Haloalkyl" refers to a lower alkyl group, an alkenyl group, an alkynyl group, a bridged cycloalkyl group, a cycloalkyl group or a heterocyclic ring, as defined herein, to which is appended one or more halogens, as defined herein. Exemplary haloalkyl groups include trifluoromethyl, chloromethyl, 2-bromobutyl, 1-bromo-2-chloro-pentyl, and the like.

"Alkenyl" refers to a branched or straight chain C_2-C_{10} hydrocarbon (preferably a C_2-C_8 hydrocarbon, more preferably a C_2-C_6 hydrocarbon) that can comprise one or more carbon-carbon double bonds. Exemplary alkenyl groups include propylenyl, buten-1-yl, isobutenyl, penten-1-yl, 2,2-methylbuten-1-yl, 3-methylbuten-1-yl, hexan-1-yl, hepten-1-yl, octen-1-yl, and the like.

"Lower alkenyl" refers to a branched or straight chain C_2-C_4 hydrocarbon that can comprise one or two carbon-carbon double bonds.

"Substituted alkenyl" refers to a branched or straight chain C_2-C_{10} hydrocarbon (preferably a C_2-C_8 hydrocarbon, more preferably a C_2-C_6 hydrocarbon) which can comprise one or more carbon-carbon double bonds, wherein one or more of the hydrogen atoms have been replaced with one or more R^{100} groups, wherein each R^{100} is independently a hydroxy, an oxo, a carboxyl, a carboxamido, a halo, a cyano or an amino group, as defined herein.

"Alkynyl" refers to an unsaturated acyclic C_2-C_{10} hydrocarbon (preferably a C_2-

C_8 hydrocarbon, more preferably a C_2-C_6 hydrocarbon) that can comprise one or more carbon-carbon triple bonds. Exemplary alkynyl groups include ethynyl, propynyl, butyn-1-yl, butyn-2-yl, pentyl-1-yl, pentyl-2-yl, 3-methylbutyn-1-yl, hexyl-1-yl, hexyl-2-yl, hexyl-3-yl, 3,3-dimethyl-butyn-1-yl, and the like.

"Bridged cycloalkyl" refers to two or more cycloalkyl groups, heterocyclic groups, or a combination thereof fused via adjacent or non-adjacent atoms. Bridged cycloalkyl groups can be unsubstituted or substituted with one, two or three substituents independently selected from alkyl, alkoxy, amino, alkylamino, dialkylamino, hydroxy, halo, carboxyl, alkylcarboxylic acid, aryl, amidyl, ester, alkylcarboxylic ester, carboxamido, alkylcarboxamido, oxo and nitro. Exemplary bridged cycloalkyl groups include adamantyl, decahydronapthyl, quinuclidyl, 2,6-dioxabicyclo(3.3.0)octane, 7-oxabicyclo(2.2.1)heptyl, 8-azabicyclo(3,2,1)oct-2-enyl and the like.

"Cycloalkyl" refers to a saturated or unsaturated cyclic hydrocarbon comprising from about 3 to about 10 carbon atoms. Cycloalkyl groups can be unsubstituted or substituted with one, two or three substituents independently selected from alkyl, alkoxy, amino, alkylamino, dialkylamino, arylamino, diarylamino, alkylarylamino, aryl, amidyl, ester, hydroxy, halo, carboxyl, alkylcarboxylic acid, alkylcarboxylic ester, carboxamido, alkylcarboxamido, oxo, alkylsulfinyl, and nitro. Exemplary cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, cyclohepta-1,3-dienyl, and the like.

"Heterocyclic ring or group" refers to a saturated or unsaturated cyclic hydrocarbon group having about 2 to about 10 carbon atoms (preferably about 4 to about 6 carbon atoms) where 1 to about 4 carbon atoms are replaced by one or more nitrogen, oxygen and/or sulfur atoms. Sulfur maybe in the thio, sulfinyl or sulfonyl oxidation state. The heterocyclic ring or group can be fused to an aromatic hydrocarbon group. Heterocyclic groups can be unsubstituted or substituted with one, two or three substituents independently selected from alkyl, alkoxy, amino, alkylthio, aryloxy, arylthio, arylalkyl, hydroxy, oxo, thial, halo, carboxyl, carboxylic ester, alkylcarboxylic acid, alkylcarboxylic ester, aryl, arylcarboxylic acid, arylcarboxylic ester, amidyl, ester, alkylcarbonyl, arylcarbonyl, alkylsulfinyl, carboxamido, alkylcarboxamido, arylcarboxamido, sulfonic acid, sulfonic ester, sulfonamide nitrate and nitro. Exemplary

heterocyclic groups include pyrrolyl, furyl, thienyl, 3-pyrrolinyl,4,5,6-trihydro-2H-pyranyl, pyridinyl, 1,4-dihydropyridinyl, pyrazolyl, triazolyl, pyrimidinyl, pyridazinyl, oxazolyl, thiazolyl, imidazolyl, indolyl, thiophenyl, furanyl, tetrahydrofuranyl, tetrazolyl, pyrrolinyl, pyrrolindinyl, oxazolindinyl 1,3-dioxolanyl, imidazolinyl, imidazolindinyl, pyrazolinyl, pyrazolidinyl, isoxazolyl, isothiazolyl, 1,2,3-oxadiazolyl, 1,2,3-triazolyl, 1,3,4-thiadiazolyl, 2H-pyranyl, 4H-pyranyl, piperidinyl, 1,4-dioxanyl, morpholinyl, 1,4-dithianyl, thiomorpholinyl, pyrazinyl, piperazinyl, 1,3,5-triazinyl, 1,3,5-trithianyl, benzo(b)thiophenyl, benzimidazolyl, benzothiazolinyl, quinolinyl, 2,6-dioxabicyclo(3.3.0)octane, and the like.

"Heterocyclic compounds" refer to mono- and polycyclic compounds comprising at least one aryl or heterocyclic ring.

"Aryl" refers to a monocyclic, bicyclic, carbocyclic or heterocyclic ring system comprising one or two aromatic rings. Exemplary aryl groups include phenyl, pyridyl, napthyl, quinoyl, tetrahydronaphthyl, furanyl, indanyl, indenyl, indoyl, and the like. Aryl groups (including bicyclic aryl groups) can be unsubstituted or substituted with one, two or three substituents independently selected from alkyl, alkoxy, alkylthio, amino, alkylamino, dialkylamino, arylamino, diarylamino, alkylarylamino, halo, cyano, alkylsulfinyl, hydroxy, carboxyl, carboxylic ester, alkylcarboxylic acid, alkylcarboxylic ester, aryl, arylcarboxylic acid, arylcarboxylic ester, alkylcarbonyl, arylcarbonyl, amidyl, ester, carboxamido, alkylcarboxamido, carbomyl, sulfonic acid, sulfonic ester, sulfonamido and nitro. Exemplary substituted aryl groups include tetrafluorophenyl, pentafluorophenyl, sulfonamide, alkylsulfonyl, arylsulfonyl, and the like.

"Cycloalkenyl" refers to an unsaturated cyclic C_2-C_{10} hydrocarbon (preferably a C_2-C_8 hydrocarbon, more preferably a C_2-C_6 hydrocarbon) which can comprise one or more carbon-carbon triple bonds.

"Alkylaryl" refers to an alkyl group, as defined herein, to which is appended an aryl group, as defined herein. Exemplary alkylaryl groups include benzyl, phenylethyl, hydroxybenzyl, fluorobenzyl, fluorophenylethyl, and the like.

"Arylalkyl" refers to an aryl radical, as defined herein, attached to an alkyl radical, as defined herein. Exemplary arylalkyl groups include benzyl, phenylethyl, 4-hydroxybenzyl, 3-fluorobenzyl, 2-fluorophenylethyl, and the like.

"Arylalkenyl" refers to an aryl radical, as defined herein, attached to an alkenyl radical, as defined herein. Exemplary arylalkenyl groups include styryl, propenylphenyl, and the like.

"Cycloalkylalkyl" refers to a cycloalkyl radical, as defined herein, attached to an alkyl radical, as defined herein.

"Cycloalkylalkoxy" refers to a cycloalkyl radical, as defined herein, attached to an alkoxy radical, as defined herein.

"Cycloalkylalkylthio" refers to a cycloalkyl radical, as defined herein, attached to an alkylthio radical, as defined herein.

"Heterocyclicalkyl" refers to a heterocyclic ring radical, as defined herein, attached to an alkyl radical, as defined herein.

"Arylheterocyclic ring" refers to a bi- or tricyclic ring comprised of an aryl ring, as defined herein, appended via two adjacent carbon atoms of the aryl ring to a heterocyclic ring, as defined herein. Exemplary arylheterocyclic rings include dihydroindole, 1,2,3,4-tetra-hydroquinoline, and the like.

"Alkylheterocyclic ring" refers to a heterocyclic ring radical, as defined herein, attached to an alkyl radical, as defined herein. Exemplary alkylheterocyclic rings include 2-pyridylmethyl, 1-methylpiperidin-2-one-3-methyl, and the like.

"Alkoxy" refers to $R_{50}O$-, wherein R_{50} is an alkyl group, as defined herein (preferably a lower alkyl group or a haloalkyl group, as defined herein). Exemplary alkoxy groups include methoxy, ethoxy, t-butoxy, cyclopentyloxy, trifluoromethoxy, and the like.

"Aryloxy" refers to $R_{55}O$-, wherein R_{55} is an aryl group, as defined herein. Exemplary arylkoxy groups include napthyloxy, quinolyloxy, isoquinolizinyloxy, and the like.

"Alkylthio" refers to $R_{50}S$-, wherein R_{50} is an alkyl group, as defined herein.

"Lower alkylthio" refers to a lower alkyl group, as defined herein, appended to a thio group, as defined herein.

"Arylalkoxy" or "alkoxyaryl" refers to an alkoxy group, as defined herein, to which is appended an aryl group, as defined herein. Exemplary arylalkoxy groups include benzyloxy, phenylethoxy, chlorophenylethoxy, and the like.

"Arylalklythio" or refers to an alkylthio group, as defined herein, to which is appended an aryl group, as defined herein. Exemplary arylalklythio groups include benzylthio, phenylethylthio, chlorophenylethylthio, and the like.

"Arylalklythioalkyl" or refers to an arylalkylthio group, as defined herein, to which is appended an alkyl group, as defined herein. Exemplary arylalklythioalkyl groups include benzylthiomethyl, phenylethylthiomethyl, chlorophenylethylthioethyl, and the like.

"Alkylthioalkyl" or refers to an alkylthio group, as defined herein, to which is appended an alkyl group, as defined herein. Exemplary alkylthioalkyl groups include allylthiomethyl, ethylthiomethyl, trifluoroethylthiomethyl, and the like.

"Alkoxyalkyl" refers to an alkoxy group, as defined herein, appended to an alkyl group, as defined herein. Exemplary alkoxyalkyl groups include methoxymethyl, methoxyethyl, isopropoxymethyl, and the like.

"Alkoxyhaloalkyl" refers to an alkoxy group, as defined herein, appended to a haloalkyl group, as defined herein. Exemplary alkoxyhaloalkyl groups include 4-methoxy-2-chlorobutyl and the like.

"Cycloalkoxy" refers to $R_{54}O$-, wherein R_{54} is a cycloalkyl group or a bridged cycloalkyl group, as defined herein. Exemplary cycloalkoxy groups include cyclopropyloxy, cyclopentyloxy, cyclohexyloxy, and the like.

"Cycloalkylthio" refers to $R_{54}S$-, wherein R_{54} is a cycloalkyl group or a bridged cycloalkyl group, as defined herein. Exemplary cycloalkylthio groups include cyclopropylthio, cyclopentylthio, cyclohexylthio, and the like.

"Haloalkoxy" refers to an alkoxy group, as defined herein, in which one or more of the hydrogen atoms on the alkoxy group are substituted with halogens, as defined herein. Exemplary haloalkoxy groups include 1,1,1-trichloroethoxy, 2-bromobutoxy, and the like.

"Hydroxy" refers to -OH.

"Oxy" refers to –O-

"Oxo " refers to =O.

"Oxylate " refers to $-O^- R_{77}^+$ wherein R_{77} is an organic or inorganic cation.

"Thiol" refers to –SH.

"Thio" refers to –S-.

"Oxime" refers to =N-OR_{81} wherein $R_{81}$is a hydrogen, an alkyl group, an aryl group, an alkylsulfonyl group, an arylsulfonyl group, a carboxylic ester, an alkylcarbonyl group, an arylcarbonyl group, a carboxamido group, an alkoxyalkyl group or an alkoxyaryl group.

"Hydrazone refers to =N-N(R_{81})(R'_{81}) wherein R'_{81} is independently selected from R_{81}, and R_{81} is as defined herein.

"Hydrazino" refers to H_2N-N(H)-.

"Organic cation" refers to a positively charged organic ion. Exemplary organic cations include alkyl substituted ammonium cations, and the like.

"Inorganic cation" refers to a positively charged metal ion. Exemplary inorganic cations include Group I metal cations such as for example, sodium, potassium, magnesium, calcium, and the like.

"Hydroxyalkyl" refers to a hydroxy group, as defined herein, appended to an alkyl group, as defined herein.

"Nitrate" refers to -O-NO_2.

"Nitrite" refers to -O-NO.

"Thionitrate" refers to -S-NO_2.

"Thionitrite" and "nitrosothiol" refer to -S-NO.

"Nitro" refers to the group -NO_2 and "nitrosated" refers to compounds that have been substituted therewith.

"Nitroso" refers to the group -NO and "nitrosylated" refers to compounds that have been substituted therewith.

"Nitrile" and "cyano" refer to -CN.

"Halogen" or "halo" refers to iodine (I), bromine (Br), chlorine (Cl), and/or fluorine (F).

"Amino " refers to -NH_2, an alkylamino group, a dialkylamino group, an arylamino group, a diarylamino group, an alkylarylamino group or a heterocyclic ring, as defined herein.

"Alkylamino" refers to R_{50}NH-, wherein R_{50} is an alkyl group, as defined herein. Exemplary alkylamino groups include methylamino, ethylamino, butylamino,

cyclohexylamino, and the like.

"Arylamino" refers to $R_{55}NH$-, wherein R_{55} is an aryl group, as defined herein.

"Dialkylamino" refers to $R_{52}R_{53}N$-, wherein R_{52} and R_{53} are each independently an alkyl group, as defined herein. Exemplary dialkylamino groups include dimethylamino, diethylamino, methyl propargylamino, and the like.

"Diarylamino" refers to $R_{55}R_{60}N$-, wherein R_{55} and R_{60} are each independently an aryl group, as defined herein.

"Alkylarylamino or arylalkylamino" refers to $R_{52}R_{55}N$-, wherein R_{52} is an alkyl group, as defined herein, and R_{55} is an aryl group, as defined herein.

"Alkylarylalkylamino " refers to $R_{52}R_{79}N$-, wherein R_{52} is an alkyl group, as defined herein, and R_{79} is an arylalkyl group, as defined herein.

"Alkylcycloalkylamino " refers to $R_{52}R_{80}N$-, wherein R_{52} is an alkyl group, as defined herein, and R_{80} is an cycloalkyl group, as defined herein.

"Aminoalkyl " refers to an amino group, an alkylamino group, a dialkylamino group, an arylamino group, a diarylamino group, an alkylarylamino group or a heterocyclic ring, as defined herein, to which is appended an alkyl group, as defined herein. Exemplary aminoalkyl groups include dimethylaminopropyl, diphenylaminocyclopentyl, methylaminomethyl, and the like.

"Aminoaryl " refers to an aryl group to which is appended an alkylamino group, a arylamino group or an arylalkylamino group. Exemplary aminoaryl groups include anilino, N-methylanilino, N-benzylanilino, and the like.

"Thio" refers to –S-.

"Sulfinyl" refers to -S(O)-.

"Methanthial" refers to -C(S)-.

"Thial" refers to =S.

"Sulfonyl" refers to $-S(O)_2^-$.

"Sulfonic acid" refers to $-S(O)_2OR_{76}$, wherein R_{76} is a hydrogen, an organic cation or an inorganic cation, as defined herein.

"Alkylsulfonic acid" refers to a sulfonic acid group, as defined herein, appended to an alkyl group, as defined herein.

"Arylsulfonic acid" refers to a sulfonic acid group, as defined herein, appended to an aryl group, as defined herein

"Sulfonic ester" refers to $-S(O)_2OR_{58}$, wherein R_{58} is an alkyl group, an aryl group, or an aryl heterocyclic ring, as defined herein.

"Sulfonamido" refers to $-S(O)_2-N(R_{51})(R_{57})$, wherein R_{51} and R_{57} are each independently a hydrogen atom, an alkyl group, an aryl group or an arylheterocyclic ring, as defined herein, or R_{51} and R_{57} when taken together are a heterocyclic ring, a cycloalkyl group or a bridged cycloalkyl group, as defined herein.

"Alkylsulfonamido" refers to a sulfonamido group, as defined herein, appended to an alkyl group, as defined herein.

"Arylsulfonamido" refers to a sulfonamido group, as defined herein, appended to an aryl group, as defined herein.

"Alkylthio" refers to $R_{50}S-$, wherein R_{50} is an alkyl group, as defined herein (preferably a lower alkyl group, as defined herein).

"Arylthio" refers to $R_{55}S-$, wherein R_{55} is an aryl group, as defined herein.

"Arylalkylthio" refers to an aryl group, as defined herein, appended to an alkylthio group, as defined herein.

"Alkylsulfinyl" refers to $R_{50}-S(O)-$, wherein R_{50} is an alkyl group, as defined herein.

"Alkylsulfonyl" refers to $R_{50}-S(O)_2-$, wherein R_{50} is an alkyl group, as defined herein.

"Alkylsulfonyloxy" refers to $R_{50}-S(O)_2-O-$, wherein R_{50} is an alkyl group, as defined herein.

"Arylsulfinyl" refers to $R_{55}-S(O)-$, wherein R_{55} is an aryl group, as defined herein.

"Arylsulfonyl" refers to $R_{55}-S(O)_2-$, wherein R_{55} is an aryl group, as defined herein.

"Arylsulfonyloxy" refers to $R_{55}-S(O)_2-O-$, wherein R_{55} is an aryl group, as defined herein.

"Amidyl" refers to $R_{51}C(O)N(R_{57})-$ wherein R_{51} and R_{57} are each independently a hydrogen atom, an alkyl group, an aryl group or an arylheterocyclic ring, as defined

herein.

"Ester" refers to $R_{51}C(O)R_{76}$- wherein R_{51} is a hydrogen atom, an alkyl group, an aryl group or an arylheterocyclic ring, as defined herein and R_{76} is oxygen or sulfur.

"Carbamoyl" refers to -O-C(O)N(R_{51})(R_{57}), wherein R_{51} and R_{57} are each independently a hydrogen atom, an alkyl group, an aryl group or an arylheterocyclic ring, as defined herein, or R_{51} and R_{57} taken together are a heterocyclic ring, a cycloalkyl group or a bridged cycloalkyl group, as defined herein.

"Carboxyl" refers to –C(O)OR_{76}, wherein R_{76} is a hydrogen, an organic cation or an inorganic cation, as defined herein.

"Carbonyl" refers to –C(O)-.

"Alkylcarbonyl" refers to R_{52}-C(O)-, wherein R_{52} is an alkyl group, as defined herein.

"Arylcarbonyl" refers to R_{55}-C(O)-, wherein R_{55} is an aryl group, as defined herein.

"Arylalkylcarbonyl" refers to R_{55}-R_{52}-C(O)-, wherein R_{55} is an aryl group, as defined herein, and R_{52} is an alkyl group, as defined herein.

"Alkylarylcarbonyl" refers to R_{52}-R_{55}-C(O)-, wherein R_{55} is an aryl group, as defined herein, and R_{52} is an alkyl group, as defined herein.

"Heterocyclicalkylcarbonyl" refer to $R_{78}C(O)$- wherein R_{78} is a heterocyclicalkyl group, as defined herein.

"Carboxylic ester" refers to -C(O)OR_{58}, wherein R_{58} is an alkyl group, an aryl group or an aryl heterocyclic ring, as defined herein.

"Alkylcarboxylic acid" and "alkylcarboxyl" refer to an alkyl group, as defined herein, appended to a carboxyl group, as defined herein.

"Alkylcarboxylic ester" refers to an alkyl group, as defined herein, appended to a carboxylic ester group, as defined herein.

"Alkyl ester" refers to an alkyl group, as defined herein, appended to an ester group, as defined herein.

"Arylcarboxylic acid" refers to an aryl group, as defined herein, appended to a carboxyl group, as defined herein.

"Arylcarboxylic ester" and "arylcarboxyl" refer to an aryl group, as defined herein, appended to a carboxylic ester group, as defined herein.

"Aryl ester" refers to an aryl group, as defined herein, appended to an ester group, as defined herein.

"Carboxamido" refers to -C(O)N(R_{51})(R_{57}), wherein R_{51} and R_{57} are each independently a hydrogen atom, an alkyl group, an aryl group or an arylheterocyclic ring, as defined herein, or R_{51} and R_{57} when taken together are a heterocyclic ring, a cycloalkyl group or a bridged cycloalkyl group, as defined herein.

"Alkylcarboxamido" refers to an alkyl group, as defined herein, appended to a carboxamido group, as defined herein.

"Arylcarboxamido" refers to an aryl group, as defined herein, appended to a carboxamido group, as defined herein.

"Urea" refers to -N(R_{59})-C(O)N(R_{51})(R_{57}) wherein R_{51}, R_{57}, and R_{59} are each independently a hydrogen atom, an alkyl group, an aryl group or an arylheterocyclic ring, as defined herein, or R_{51} and R_{57} taken together are a heterocyclic ring, a cycloalkyl group or a bridged cycloalkyl group, as defined herein.

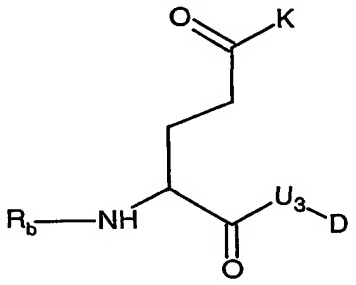
"Phosphoryl" refers to -P(R_{70})(R_{71})(R_{72}), wherein R_{70} is a lone pair of electrons, thial or oxo, and R_{71} and R_{72} are each independently a covalent bond, a hydrogen, a lower alkyl, an alkoxy, an alkylamino, a hydroxy, an oxy or an aryl, as defined herein.

"Silyl" refers to -Si(R_{73})(R_{74})(R_{75}), wherein R_{73}, R_{74} and R_{75} are each independently a covalent bond, a lower alkyl, an alkoxy, an aryl or an arylalkoxy, as defined herein.

The invention is directed to the targeted delivery of the compounds of the invention and nitric oxide to organs, cells or tissues containing the enzyme gamma-glutamyl transpeptidase and to methods for (a) treating cardiovascular diseases; (b) treating renovascular diseases; (c) treating diabetes; (d) treating diseases resulting from oxidative stress; (e) treating endothelial dysfunctions; (f) treating diseases caused by endothelial dysfunctions; (g) treating cirrhosis; (h) treating pre-eclampsia; (j) treating osteoporosis; (k) treating nephropathy; (l) treating diseases resulting from elevated levels of gamma-glutamyl transpeptidase and (m) the targeted delivery of compounds and nitric oxide to organs, cells or tissues containing the enzyme gamma-glutamyl

transpeptidase by administering one or more compounds of the invention, that are linked (directly or indirectly) to one or more nitric oxide adducts. The glutamic acid compounds of the invention are nitrosated through one or more of these functionalities such as oxygen (hydroxyl condensation), sulfur (sulfhydryl condensation) and/or nitrogen. Preferably, the compounds of the invention are administered in the form of a pharmaceutical composition that further comprise a pharmaceutically acceptable carrier or diluent. The novel compounds and novel compositions of the invention are described in more detail herein.

In one embodiment, the invention describes nitrosated glutamic acid compounds and pharmaceutically acceptable salts thereof, of Formula (I):



(I)

wherein:

R_b is a hydrogen or a lower alkyl group;

D is a hydrogen, V_3 or K;

U_3 at each occurrence is independently an oxygen, $-S(O)_o-$ or $-N(R_a)R_i$;

o is an integer from 0 to 2;

K is $-(W_3)_a-E_b-(C(R_e)(R_f))_{p1}-E_c-(C(R_e)(R_f))_x-(W_3)_d-(C(R_e)(R_f))_y-(W_3)_i-E_j-(W_3)_g-(C(R_e)(R_f))_z-U_3-V_3$;

V_3 is a hydrogen or $-NO_2$;

a, b, c, d, g, i and j are each independently an integer from 0 to 3;

p_1, x, y and z are each independently an integer from 0 to 10;

W_3 at each occurrence is independently -C(O)-, -C(S)-, $-T_3-$, $-(C(R_e)(R_f))_h-$, an alkyl group, an aryl group, a heterocyclic ring, an arylheterocyclic ring, or $-(CH_2CH_2O)_{q1}-$;

E at each occurrence is independently $-T_3-$, an alkyl group, an aryl group, $-(C(R_e)(R_f))_h-$, a heterocyclic ring, an arylheterocyclic ring, or $-(CH_2CH_2O)_{q1}-$;

T_3 at each occurrence is independently a covalent bond, a carbonyl, an oxygen, -$S(O)_o$- or -$N(R_a)R_i$;

h is an integer form 1 to 10;

q_1 is an integer from 1 to 5;

R_e and R_f are each independently a hydrogen, an alkyl, a cycloalkoxy, a halogen, a hydroxy, an hydroxyalkyl, an alkoxyalkyl, an arylheterocyclic ring, an alkylaryl, an alkylcycloalkyl, an alkylheterocyclic ring, a cycloalkylalkyl, a cycloalkylthio, an arylalklythio, an arylalklythioalkyl, an alkylthioalkyl a cycloalkenyl, an heterocyclicalkyl, an alkoxy, a haloalkoxy, an amino, an alkylamino, a dialkylamino, an arylamino, a diarylamino, an alkylarylamino, an alkoxyhaloalkyl, a sulfonic acid, a sulfonic ester, an alkylsulfonic acid, an arylsulfonic acid, an arylalkoxy, an alkylthio, an arylthio, a cyano an aminoalkyl, an aminoaryl, an aryl, an arylalkyl, an alkylaryl, a carboxamido, a alkylcarboxamido, an arylcarboxamido, an amidyl, a carboxyl, a carbamoyl, an alkylcarboxylic acid, an arylcarboxylic acid, an alkylcarbonyl, an arylcarbonyl, an ester, a carboxylic ester, an alkylcarboxylic ester, an arylcarboxylic ester, a sulfonamido, an alkylsulfonamido, an arylsulfonamido, an alkylsulfonyl, an alkylsulfonyloxy, an arylsulfonyl, arylsulphonyloxy, a sulfonic ester, an alkyl ester, an aryl ester, a urea, a phosphoryl, a nitro or K; or R_e and R_f taken together with the carbons to which they are attached form a carbonyl, a methanthial, a heterocyclic ring, a cycloalkyl group, an aryl group, an oxime, a hydrazone or a bridged cycloalkyl group;

R_a is a lone pair of electrons, a hydrogen or an alkyl group;

R_i is a hydrogen, an alkyl, an aryl, an alkylcarboxylic acid, an arylcarboxylic acid, an alkylcarboxylic ester, an arylcarboxylic ester, an alkylcarboxamido, an arylcarboxamido, an alkylaryl, an alkylsulfinyl, an alkylsulfonyl, an alkylsulfonyloxy, an arylsulfinyl, an arylsulfonyl, arylsulphonyloxy, a sulfonamido, a carboxamido, a carboxylic ester, an aminoalkyl, an aminoaryl, -CH_2-$C(U_3$-$V_3)(R_e)(R_f)$, a bond to an adjacent atom creating a double bond to that atom, -$(N_2O_2$-$)^-$•M_1^+, wherein M_1^+ is an organic or inorganic cation; and

with the proviso that the compounds of Formula (I) must contain least one of a nitrate or a thionitrate group.

In cases where multiple designations of variables which reside in sequence are

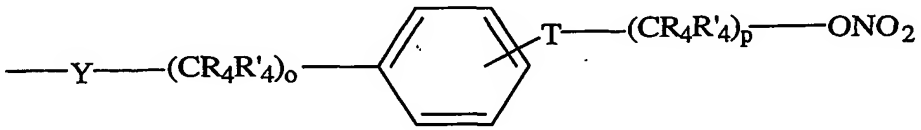
chosen as a "covalent bond" or the integer chosen is 0, the intent is to denote a single covalent bond connecting one radical to another. For example, E_0 would denote a covalent bond, while E_2 denotes (E-E) and $(C(R_4)(R_4))_2$ denotes $-C(R_4)(R_4)-C(R_4)(R_4)-$

Compounds of the invention that have one or more asymmetric carbon atoms may exist as the optically pure enantiomers, pure diastereomers, mixtures of enantiomers, mixtures of diastereomers, racemic mixtures of enantiomers, diastereomeric racemates or mixtures of diastereomeric racemates. It is to be understood that the invention anticipates and includes within its scope all such isomers and mixtures thereof.

In one embodiment of the invention for the nitrosated compounds of Formula (I), and pharmaceutically acceptable salts thereof, K is:

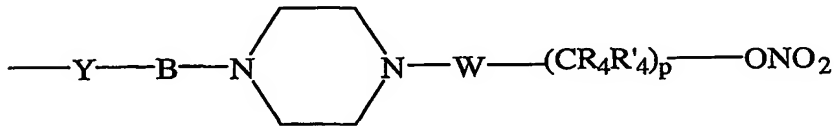
(1) $-Y-(CR_4R_4')_p-T-(CR_4R_4')_p-ONO_2$;

(2)



wherein T is ortho, meta or para;

(3)



(4) $-Y-(CR_4C_4')_p-V-B-T-(CR_4R_4')_p-ONO_2$;

(5) $-Y-(CR_4R_4')_p-T-C(O)-(CR_4R_4')_k-(CH_2)-ONO_2$;

(6) $-Y-(CR_4R_4')_p-C(Z)-(CH_2)_q-T-(CR_4R_4')_q-(CH_2)-ONO_2$;

(7) $-Y-(CR_4R_4')_p-T-(CH_2)_q-V-(CR_4R_4')_q-(CH_2)-ONO_2$;

(8) $-Y-(CR_4R_4')_p-V-(CH_2)_q-V-(CR_4R_4')_q-(CH_2)-ONO_2$;

(9) $-Y-(CR_4R_4')_k-(W)_q-(CR_4R_4')_k-(CH_2)-ONO_2$;

(10) $-NR_j-O-(CH_2)_k-V-(CR_4R_4')_q-(CH_2)-ONO_2$;

(11) $-NR_j-O-(CH_2)_k-(W)_q-(CR_4R_4')_q-(CH_2)-ONO_2$;

(12) $-O-NR_j-(CH_2)_k-(W)_q-(CR_4R_4')_q-(CH_2)-ONO_2$;

(13) $-Y-(CH_2)_k-(W)_q-(CH_2)_k-V-(CR_4R_4')_k-Q'-(CR_4R_4')_k-(CH_2)-ONO_2$;

(14) $-Y-(CR_4R_4')_p-V-(CH_2)_k-(W)_q-(CR_4R_4')_q-(CH_2)-ONO_2$;

(15) $-O-NR_j-(CH_2)_k-V-(CR_4R_4')_q-(CH_2)-ONO_2$;

(16) $-Y-(CR_4R_4')_k-Q'-(CR_4R_4')_k-V-(CR_4R_4')_k-(CH_2)-ONO_2$;

(17) $-Y-(CR_4R_4')_k-Q'-(CR_4R_4')_k-(W)_q-(CR_4R_4')_k-(CH_2)-ONO_2$;

(18) $-Y-(CR_4R_4')_p-T-(CR_4R_4')_p-Q'-(CR_4R_4')_k-(CH_2)-ONO_2$;

(19) $-Y-(CR_4R_4')_q-C(Z)-(CR_4R_4')_k-(CH_2)-ONO_2$;

(20) $-Y-(CR_4R_4')_p-Q'-(CR_4R_4')_k-(CH_2)-ONO_2$;

(21) $-Y-(CR_4R_4')_q-P(O)MM'$;

(22) $-Y-(CR_4R_4')_k-Q'-(CR_4R_4')_k-(CH_2)-ONO_2$;

(23) $-Y-(CR_4R_4')_k-Q'-(CR_4R_4')_k-T-(CR_4R_4')_k-(CH_2)-ONO_2$;

(24) $-Y-(CR_4R_4')_q-(W)_q-(CR_4R_4')_k-Q'-(CR_4R_4')_k-(CH_2)-ONO_2$;

(25) $-Y-(CR_4R_4')_q-V-(CR_4R_4')_k-Q'-(CR_4R_4')_k-(CH_2)-ONO_2$;

(26) $-Y-(CR_4R_4')_p-(T)_o-(W)_q-(CR_4R_4')_k-(CH_2)-ONO_2$;

(27) $-Y-(CR_4R_4')_p-(W)_q-(T)_o-(CR_4R_4')_k-(CH_2)-ONO_2$;

(28) $-Y-(CR_4R_4')_q-C(Z)-V-(CR_4R_4')_q-(CH_2)-ONO_2$;

(29) $-Y-(CR_4R_4')_k-C(R_4)(ONO_2)-(CR_4R_4')_q-(T)_o-(W)_q-(T)_o-(CR_4R_4')_k-R_5$;

(30) $-Y-(CR_4R_4')_k-V-(CR_4R_4')_k-Q'-(CR_4R_4')_k-(CH_2)-ONO_2$;

(31) $-Y-(CR_4R_4')_q-C(Z)-Q'-(CR_4R_4')_k-(CH_2)-ONO_2$;

(32) $-Y-(CR_4R_4')_p-V-(CR_4R_4')_p-(CH_2)-ONO_2$;

(33) $-Y-(CR_4R_4')_p-V-(CH_2)_q-(T)_o-(CR_4R_4')_q-(CH_2)-ONO_2$;

(34) $-Y-(CR_4R_4')_p-(T)_o-Q'-(T)_o-(CR_4R_4')_q-(CH_2)-ONO_2$;

(35) $-Y-(CR_4R_4')_q-C(Z)-(CR_4R_4')_q-V-(CR_4R_4')_k-Q'-(CR_4R_4')_k-(CH_2)-ONO_2$;

(36) $-Y-(CR_4R_4')_q-C(Z)-(CR_4R_4')_q-(W)_q-(CR_4R_4')_k-Q'-(CR_4R_4')_k-(CH_2)-ONO_2$;

(37) $-NR_j-O-(CH_2)_k-V-(CR_4R_4')_k-Q'-(CH_2)-ONO_2$;

(38) $-NR_j-O-(CH_2)_k-(W)_q-(CR_4R_4')_k-Q'-(CH_2)-ONO_2$;

(39) $-O-NR_j-(CH_2)_k-(W)_q-(CR_4R_4')_k-Q'-(CH_2)-ONO_2$;

(40) $-O-NR_j-(CH_2)_k-V-(CR_4R_4')_k-Q'-(CH_2)-ONO_2$;

(41) $-NR_j-NR_j-(CR_4R_4')_p-(W)_q-(T)_o-(CR_4R_4')_k-(CH_2)-ONO_2$; or

(42) $-Y-(CR_4R_4')_k-Q'-(CR_4R_4')_k-ONO_2$; or

(43) $-Y-(CR_4R_4')_k-V-(CR_4R_4')_k-Q-(CR_4R_4')_k-ONO_2$;

R_4 and R_4' at each occurrence are independently a hydrogen, lower alkyl group, -OH, $-CH_2OH$, $-ONO_2$, $-NO_2$ or $-CH_2ONO_2$; or R_4 and R_4' taken together with the carbon atom to which they are attached are a cycloalkyl group or a heterocyclic ring;

V is -C(O)-T-, -T-C(O)-, -T-C(O)-T or T-C(O)-C(O)-T;

W is a covalent bond or a carbonyl group;

T at each occurrence is independently an oxygen, $(S(O)_o)_o$ or NR_j;

R_j is a hydrogen, an alkyl group, an aryl group, a heterocyclic ring, an alkylcarbonyl group, an alkylaryl group, an alkylsulfinyl group, an alkylsulfonyl group, an arylsulfinyl group, an arylsulfonyl group, a sulfonamido group, a N-alkylsulfonamido group, a N,N-diarylsulfonamido group, a N-arylsulfonamido group, a N-alkyl-N-arylsulfonamido group, a carboxamido group or a hydroxyl group;

p at each occurrence is independently an integer from 1 to 6;

q at each occurrence is independently an integer from 1 to 3;

o at each occurrence is independently an integer from 0 to 2;

k at each occurrence is independently an integer from 0 to 4;

Y is independently a covalent bond, a carbonyl, an oxygen, $-S(O)_o-$ or $-NR_j$;

B is either phenyl or $(CH_2)_o$;

Q' is a cycloalkyl group, a heterocyclic ring or an aryl group;

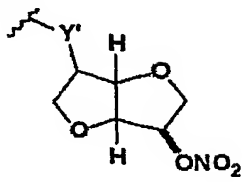
Z is (=O), $(=N-OR_5)$, $(=N-NR_5R'_5)$ or $(=CR_5R'_5)$;

M and M' are each independently $-O^- H_3N^+-(CR_4R'_4)_q-CH_2ONO_2$ or $-T-(CR_4R'_4)_k-CH_2ONO_2$; and

R_5 and R_5' at each occurrence are independently a hydrogen, a hydroxyl group, an alkyl group, an aryl group, an alkylsulfonyl group, an arylsulfonyl group, a carboxylic ester, an alkylcarbonyl group, an arylcarbonyl group, a carboxamido group, an alkoxyalkyl group, an alkoxyaryl group, a cycloalkyl group or a heterocyclic ring.

In one embodiment of the invention for the compounds of Formula (I), and pharmaceutically acceptable salts thereof, K is:

(1)



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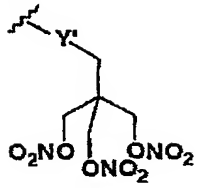

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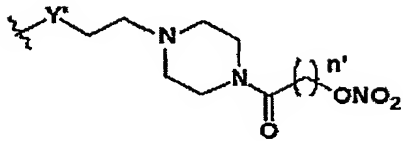

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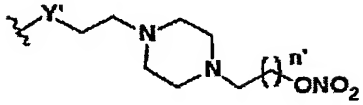

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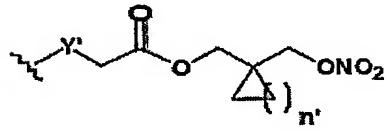

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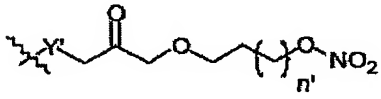

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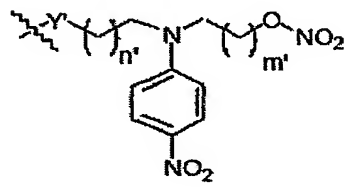

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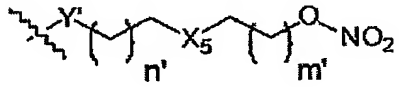

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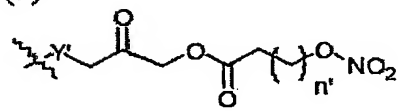

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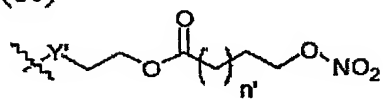

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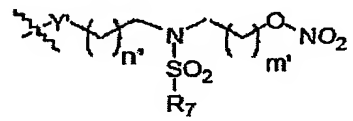

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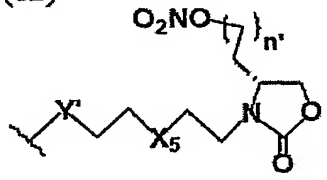

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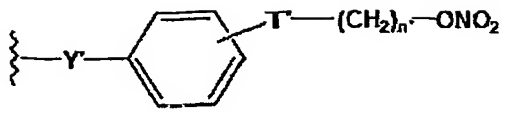

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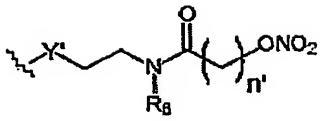
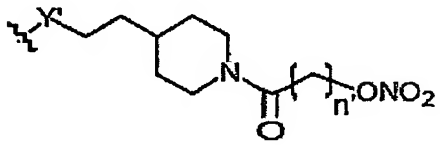


wherein T' maybe ortho, meta or para

(15)



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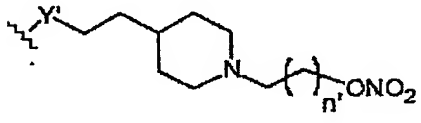

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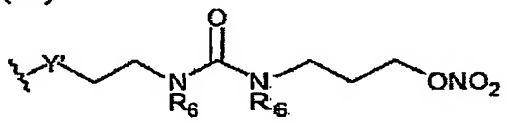

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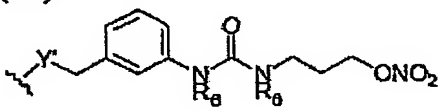

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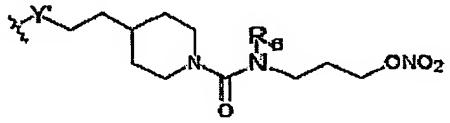

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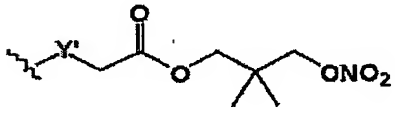

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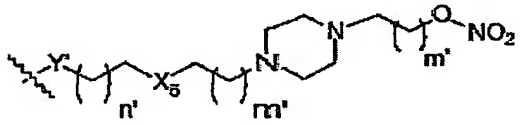

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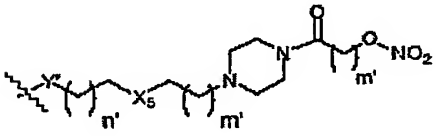

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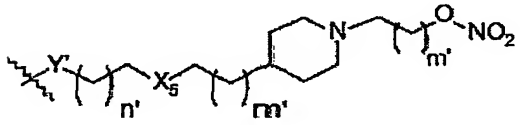

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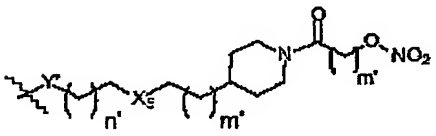

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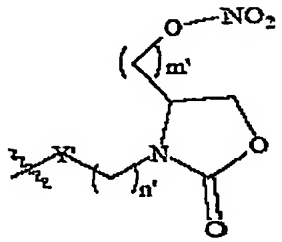

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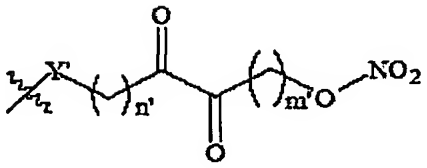

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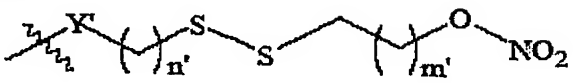

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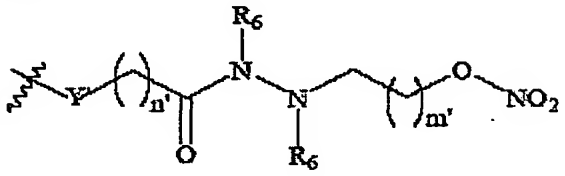

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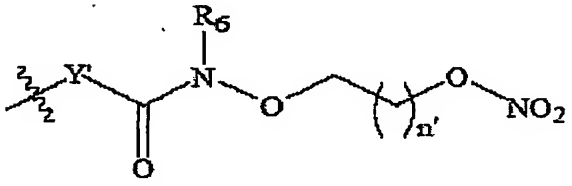

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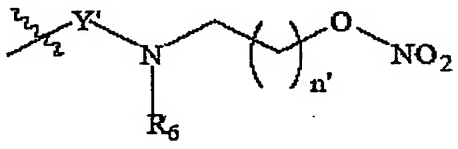

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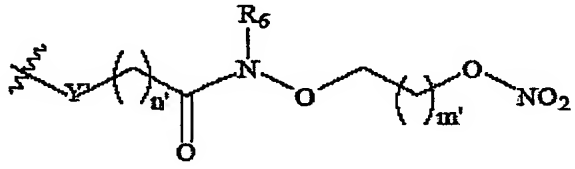

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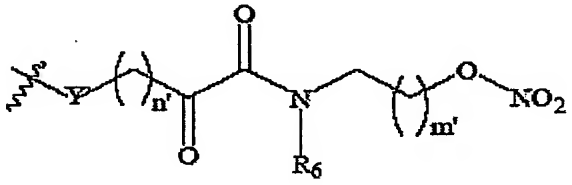

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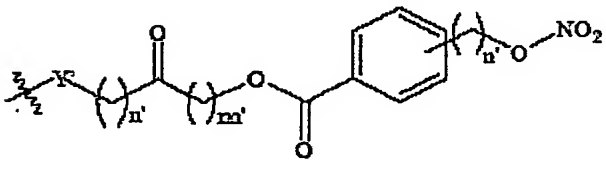

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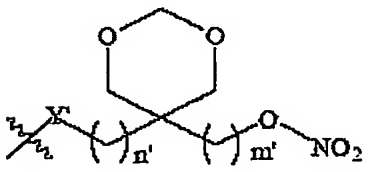

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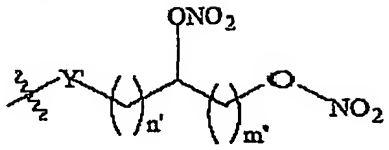

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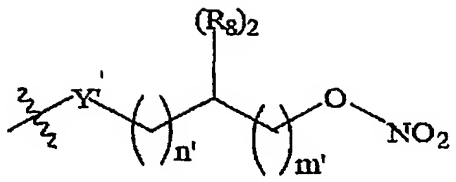

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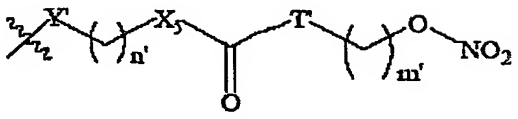

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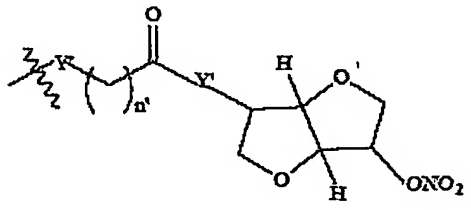

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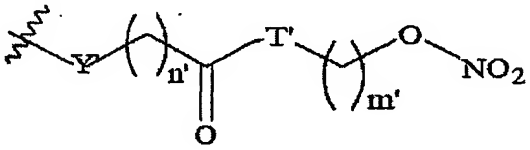

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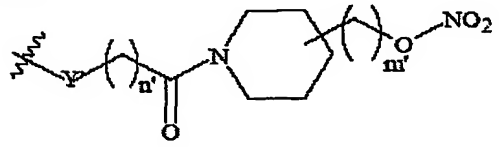

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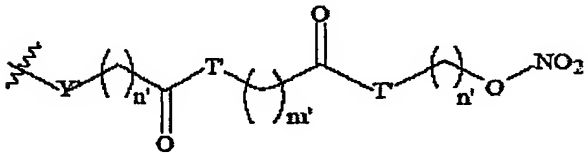

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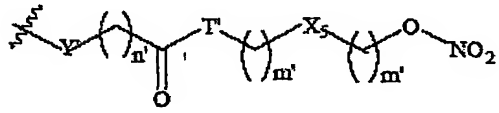

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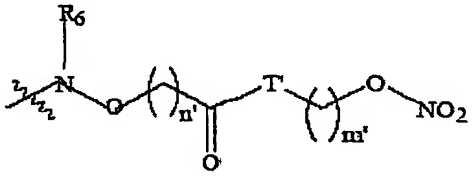

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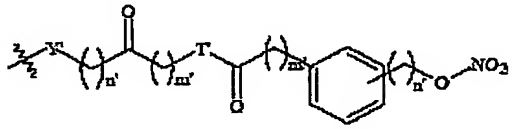

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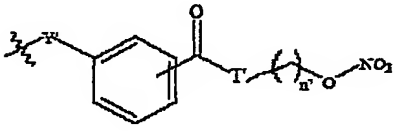

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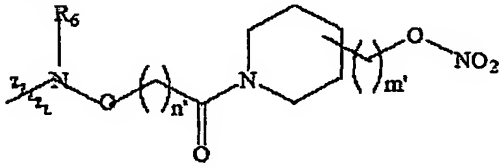

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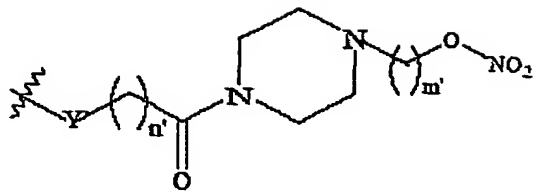

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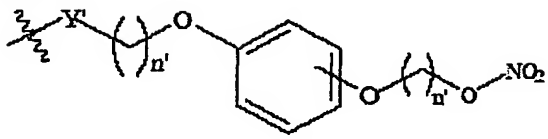

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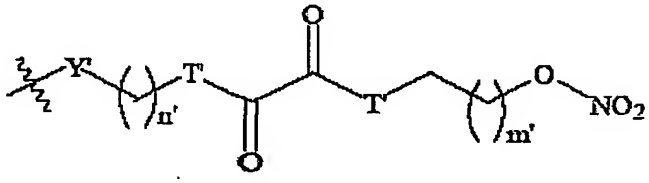

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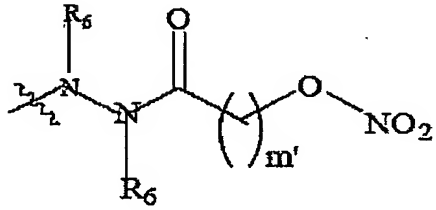

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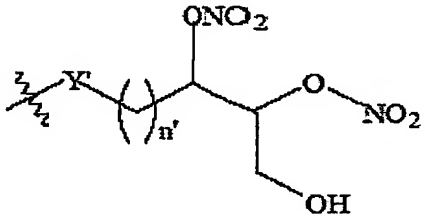

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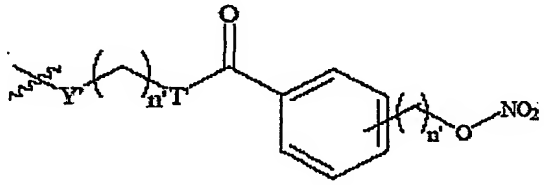

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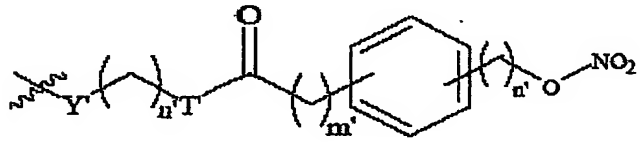

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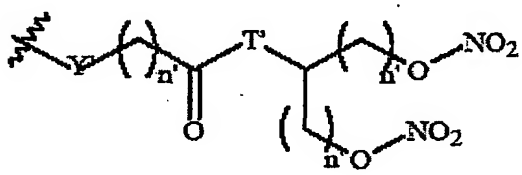

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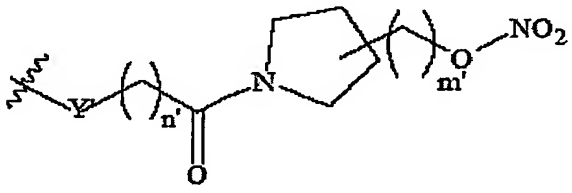

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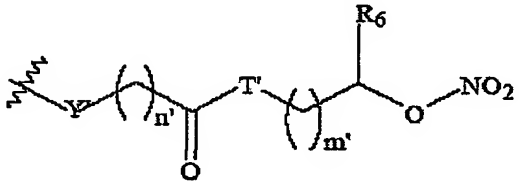


wherein:

Y' a covalent bond, a carbonyl, an oxygen, $-S(O)_o-$ or $-NR_6$;

T' is oxygen, sulfur or NR_6;

X_5 is oxygen, $(S(O)_o)_o$ or NR_6;

R_6 is a hydrogen, a lower alkyl group, an aryl group;

R_7 is a lower alkyl group or an aryl group;

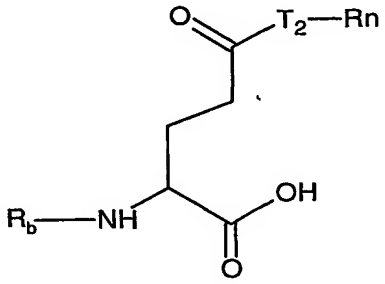
R_8 at each occurrence is independently is a hydrogen, a hydroxyl group, a lower alkyl group, an aryl group, $-NO_2$, $-CH_2-ONO_2$ or $-CH_2-OH$;

n' and m' are each independently an integer from 0 to 10; and

o is an integer from 0 to 2.

In other embodiments the nitrosated glutamic acid compound of Formula (I) is a compound of Formula (II) or a pharmaceutically acceptable salt thereof,

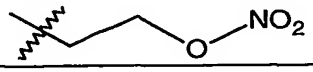
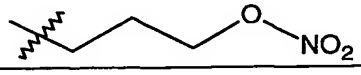
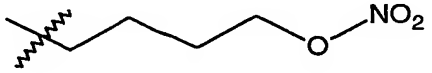
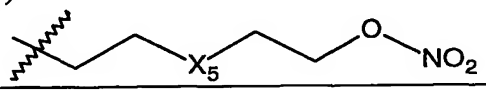
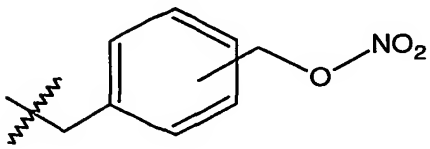
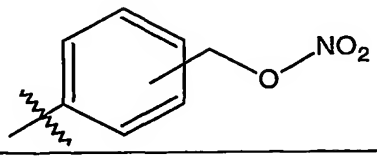
wherein the compound of Formula (II) is:

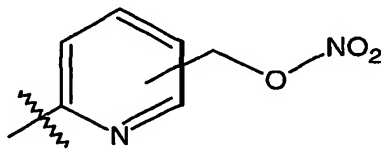
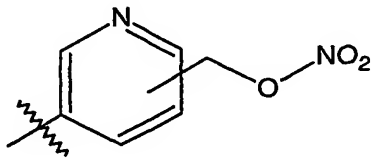
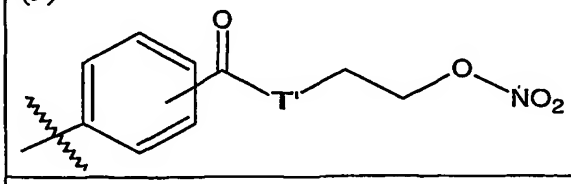
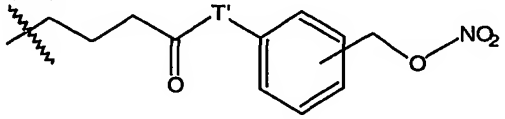
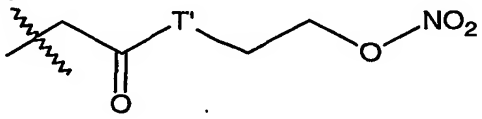
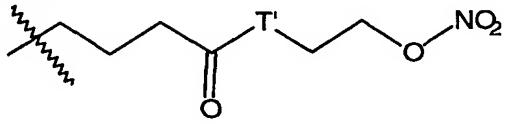
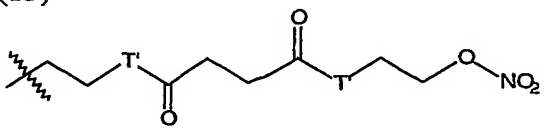
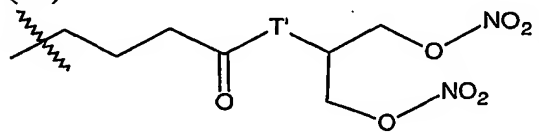
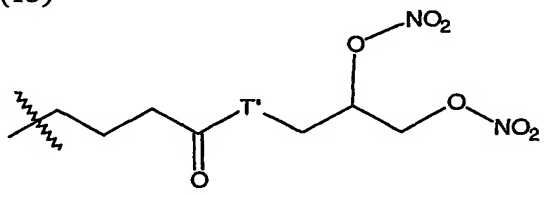
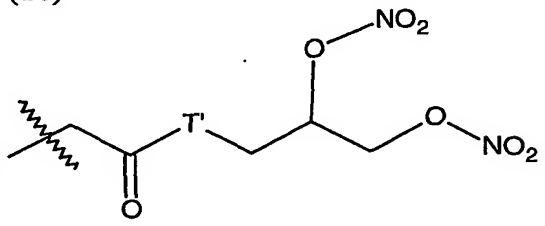
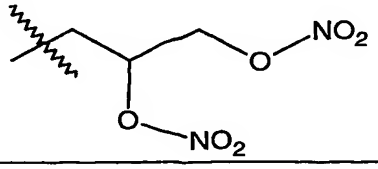
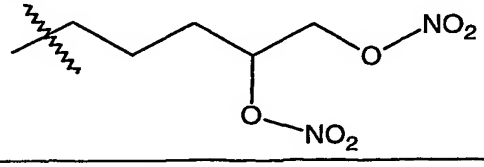


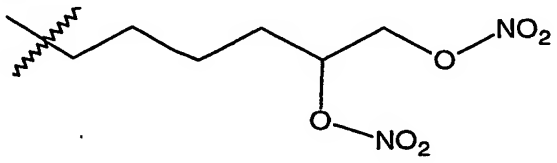
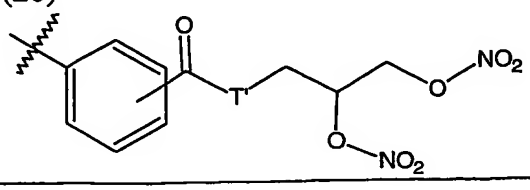
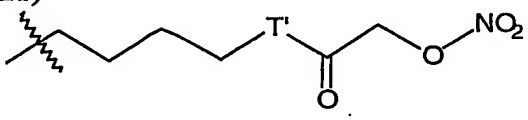
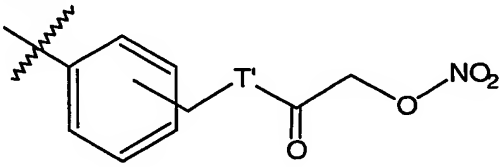
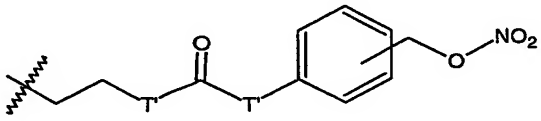
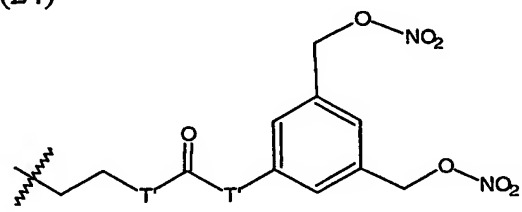
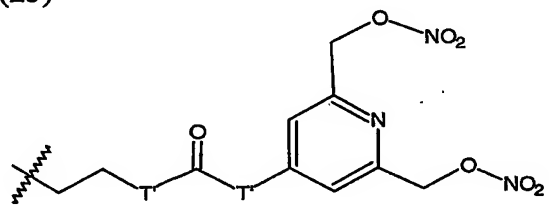
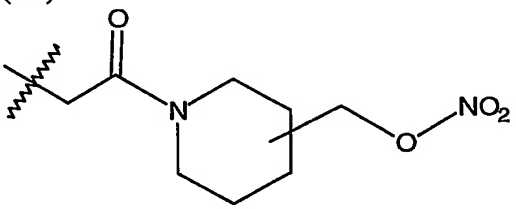
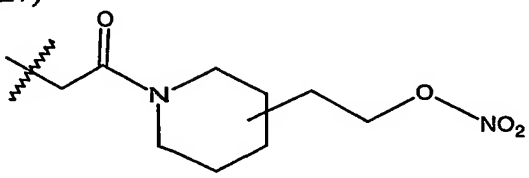
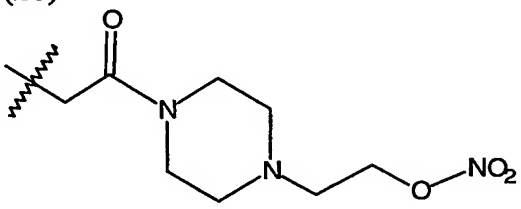
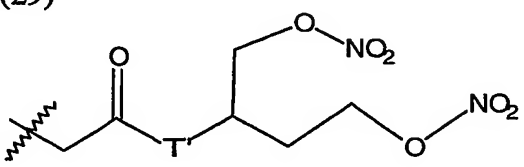
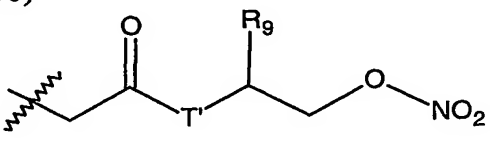
(II)

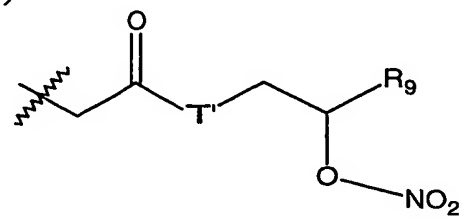
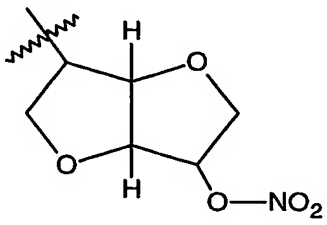
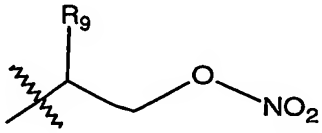
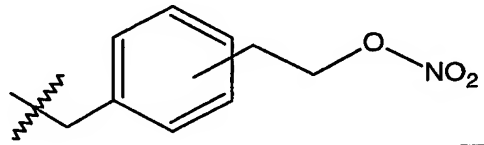
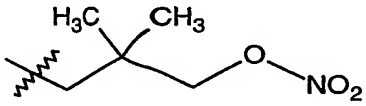
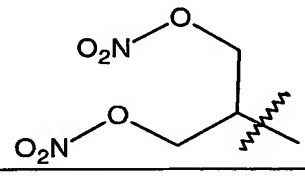
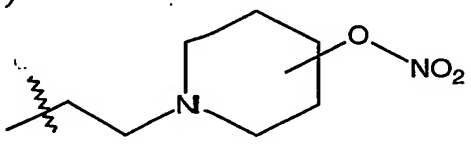
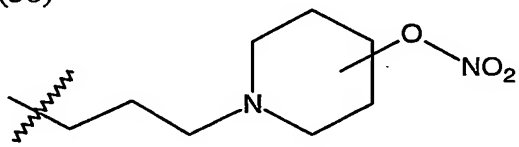
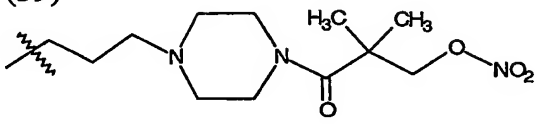
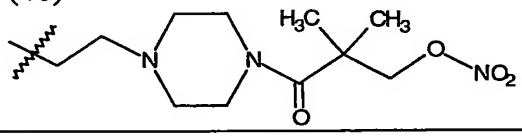
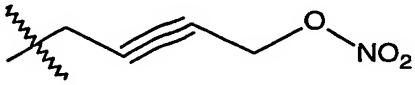
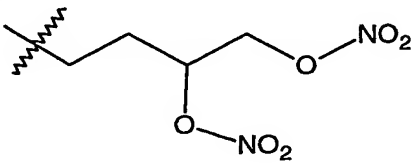
wherein

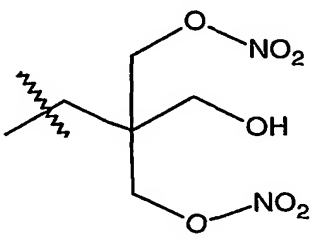
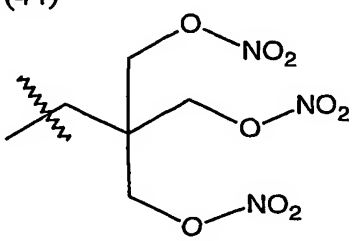
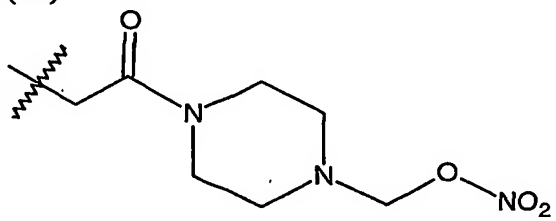
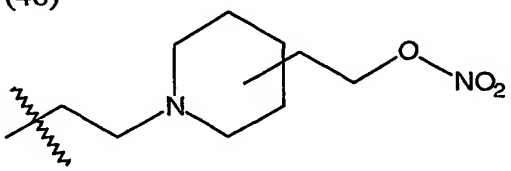
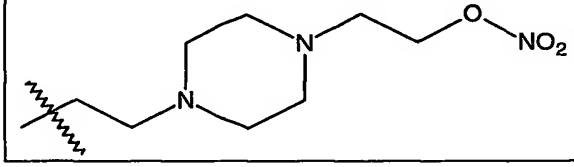
R_n is

(1) 	(2) 
(3) 	(4) 
(5) 	(6) 

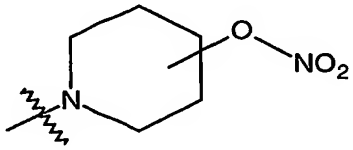
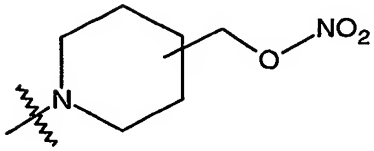
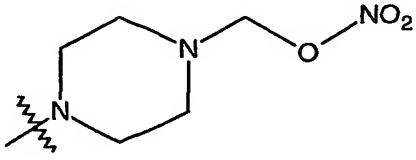
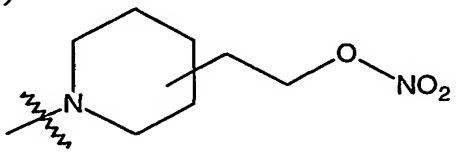
(7) 	(8) 
(9) 	(10) 
(11) 	(12) 
(13) 	(14) 
(15) 	(16) 
(17) 	(18) 

(19) 	(20) 
(21) 	(22) 
(23) 	(24) 
(25) 	(26) 
(27) 	(28) 
(29) 	(30) 

(31) 	(32) 
(33) 	(34) 
(35) 	(36) 
(37) 	(38) 
(39) 	(40) 
(41) 	(42) 

(43)  or	(44) 
(45) 	(46)  or
(47) 	

or T_2-Rn taken together are:

(1) 	(2) 
(3) 	(4)  or

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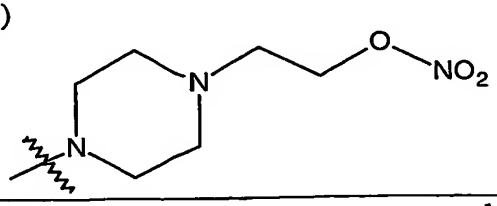
(5) 	

R_9 is a lower alkyl group or an aryl group;

T_2 is oxygen, sulfur, NR_6 or $N(R_{10})(R_{11})$;

R_{10} and R_{11} taken together are a heterocyclic ring; and

X_5, R_b and R_6 are as defined herein.

In preferred embodiments the compounds of Formulas (I) are:

(2S)-4-{[(1S,2S,5S,6R)-6-(nitrooxy)-4,8-dioxabicyclo[3.3.0]oct-2-yl]oxycarbonyl}-2-aminobutanoic acid, hydrochloride salt;

4-{{(2R)-2,3-bis(nitrooxy)propyl]oxycarbonyl}(2S)-2-aminobutanoic acid, hydrochloride salt;

(2S)-2-amino-4-{[2-(nitrooxy)ethyl]oxycarbonyl}butanoic acid, 2,2,2-trifluoroacetic acid;

(2S)-2-amino-4-[(2-(nitrooxy)ethyl]sulfonyl}ethyl)oxycarbonyl] butanoic acid, hydrochloride salt;

(2S)-2-amino-5-{4-[2-(nitrooxy)ethyl]piperidyl}-5-oxopentanoic acid; hydrochloride salt;

(2S)-4-{[(2S)-2,3-bis(nitrooxy)propyl]oxycarbonyl}-2-aminobutanoic acid, hydrochloride salt;

(2S)-2-amino-4-[({4-[2-(nitrooxy)ethyl]phenyl}methyl) oxycarbonyl]butanoic acid, hydrochloride salt;

(2S)-2-amino-4-{N-[3-(nitrooxy)propyl]carbamoyl}butanoic acid, hydrochloride salt;

(2S)-2-amino-4-{N-[2,2-dimethyl-3-(nitrooxy)propyl]carbamoyl} butanoic acid, hydrochloride salt;

(2S)-2-amino-4-{[3-(nitrooxy)propyl]oxycarbonyl}butanoic acid, hydrochloride salt;

(2S)-2-amino-4-(N-{2-[2-(nitrooxy)ethoxy]ethyl}carbamoyl)butanoic acid, hydrochloride salt;

(2S)-2-amino-4-({2-(nitrooxy)-1-[(nitrooxy)methyl]ethyl} oxycarbonyl)butanoic acid, hydrochloride salt;

(2S)-2-amino-4-{[2,2-dimethyl-3-(nitrooxy)propyl]oxycarbonyl} butanoic acid, hydrochloride salt;

tert-butyl (2S)-2-[(tert-butoxy)carbonylamino]-4-(N-{2-(nitrooxy)-1-[(nitrooxy)methyl]ethyl}carbamoyl)butanoate;

(2S)-2-amino-4-[({4-[(nitrooxy)methyl]phenyl}methyl) oxycarbonyl]butanoic acid, hydrochloride salt;

(2S)-2-amino-5-[4-(nitrooxy)piperidyl]-5-oxopentanoic acid, hydrochloride salt;

(2S)-2-amino-4-({2-[4-(nitrooxy)piperidyl]ethyl}oxycarbonyl) butanoic acid, hydrochloride salt;

(2S)-2-amino-4-{[4-(nitrooxy)but-2-ynyl]oxycarbonyl}butanoic acid, hydrochloride salt

(2S)-4-{N-[(2S)-2,3-bis(nitrooxy)propyl]carbamoyl}-2-aminobutanoic acid, hydrochloride salt;

(2S)-2-amino-5-{4-[(nitrooxy)methyl]oiperidyl}-5-oxopentanoic acid, hydrochloride salt

(2*S*)-2-amino-5-{3-[4-(nitrooxy)piperidin-1-yl]propoxy}-5-oxopentanoic acid dihydrochloride salt

(2S)-2-amino-5-{3-[(nitrooxy)methyl]piperidyl}-5-oxopentanoic acid, hydrochloride salt;

(2S)-2-amino-4-[(3-{4-[2,2-dimethyl-3-(nitrooxy)propanoyl] piperazinyl} propyl)oxycarbonyl]butanoic acid; bis hydrochloride salt;

4-{[(3R)-3,4-bis(nitrooxy)butyl]oxycarbonyl}(2S)-2-aminobutanoic acid, hydrochloride salt;

(2S)-2-amino-4-({2,2-bis[(nitrooxy)methyl]-3-hydroxypropyl} oxycarbonyl)butanoic acid, hydrochloride salt;

(2S)-2-amino-4-({2,2-bis[(nitrooxy)methyl]-3-(nitrooxy)propyl}oxycarbonyl)butanoic acid, hydrochloride salt;

(2S)-2-amino-4-{[4,5-bis(nitrooxy)pentyl]oxycarbonyl}butanoic acid, hydrochloride salt;

(2S)-2-amino-4-[(2-{4-[2,2-dimethyl-3-(nitrooxy)propanoyl] piperazinyl} ethyl)oxycarbonyl]butanoic acid, bis hydrochloride salt.

Another embodiment of the invention describes the metabolites of the nitrosated

glutamic acid compounds and pharmaceutically acceptable salts thereof. These metabolites, include but are not limited to, the non-nitrosated derivatives, degradation products, hydrolysis products, and the like, of the nitrosated glutamic acid compounds and pharmaceutically acceptable salts thereof.

Another embodiment of the invention provides processes for making the novel compounds of the invention and to the intermediates useful in such processes. The reactions are performed in solvents appropriate to the reagents and materials used are suitable for the transformations being effected. It is understood by one skilled in the art of organic synthesis that the functionality present in the molecule must be consistent with the chemical transformation proposed. This will, on occasion, necessitate judgment by the routineer as to the order of synthetic steps, protecting groups required, and deprotection conditions. Substituents on the starting materials may be incompatible with some of the reaction conditions required in some of the methods described, but alternative methods and substituents compatible with the reaction conditions will be readily apparent to one skilled in the art. The use of sulfur and oxygen protecting groups is well known for protecting thiol and alcohol groups against undesirable reactions during a synthetic procedure and many such protecting groups are known and described by, for example, Greene and Wuts, *Protective Groups in Organic Synthesis*, Third Edition, John Wiley & Sons, New York (1999).

The chemical reactions described herein are generally disclosed in terms of their broadest application to the preparation of the compounds of this invention. Occasionally, the reactions may not be applicable as described to each compound included within the disclosed scope. The compounds for which this occurs will be readily recognized by one skilled in the art. In all such cases, either the reactions can be successfully performed by conventional modifications known to one skilled in the art, *e.g.*, by appropriate protection of interfering groups, by changing to alternative conventional reagents, by routine modification of reaction conditions, and the like, or other reactions disclosed herein or otherwise conventional, will be applicable to the preparation of the corresponding compounds of this invention. In all preparative methods, all starting materials are known or readily prepared from known starting materials.

The glutamic acid compounds are nitrosated through one or more sites such as oxygen, sulfur and/or nitrogen using conventional methods known to one skilled in the art. For example, known methods for nitrosating compounds are described in U.S. Patent Nos. 5,380,758, 5,859,053, 5,703,073 and 6,297,260; and in WO 94/03421, WO 94/04484, WO 94/12463, WO 95/09831, WO 95/19952, WO 95/30641, WO 97/27749, WO 98/19672, WO 98/21193, WO 00/51988, WO 00/61604, WO 00/72838, WO 01/00563, WO 01/04082, WO 01/10814, WO 01/12584, WO 01/45703, WO 00/61541, WO 00/61537, WO 02/11707, WO 02/30866 and in Oae et al, *Org. Prep. Proc. Int.*, *15*(3):165-198 (1983), the disclosures of each of which are incorporated by reference herein in their entirety. The methods of nitrosating the compounds described in these references can be applied by one skilled in the art to produce any of the nitrosated glutamic acid compounds described herein. The nitrosated glutamic acid compounds of the invention donate, transfer or release a biologically active form of nitrogen monoxide (i.e., nitric oxide).

Nitrogen monoxide can exist in three forms: NO- (nitroxyl), NO• (nitric oxide) and NO^+ (nitrosonium). NO• is a highly reactive short-lived species that is potentially toxic to cells. This is critical because the pharmacological efficacy of NO depends upon the form in which it is delivered. In contrast to the nitric oxide radical (NO•), nitrosonium (NO^+) does not react with O_2 or O_2- species, and functionalities capable of transferring and/or releasing NO^+ and NO- are also resistant to decomposition in the presence of many redox metals. Consequently, administration of charged NO equivalents (positive and/or negative) does not result in the generation of toxic by-products or the elimination of the active NO moiety.

The term "nitric oxide" encompasses uncharged nitric oxide (NO•) and charged nitrogen monoxide species, preferably charged nitrogen monoxide species, such as nitrosonium ion (NO^+) and nitroxyl ion (NO-). The reactive form of nitric oxide can be provided by gaseous nitric oxide. The nitrogen monoxide releasing, delivering or transferring compounds have the structure F-NO, wherein F is a nitrogen monoxide releasing, delivering or transferring moiety, and include any and all such compounds which provide nitrogen monoxide to its intended site of action in a form active for its intended purpose. The term "NO adducts" encompasses any nitrogen monoxide

releasing, delivering or transferring compounds, including, for example, S-nitrosothiols, nitrites, nitrates, S-nitrothiols, sydnonimines, 2-hydroxy-2-nitrosohydrazines, (NONOates), (E)-alkyl-2-((E)- hydroxyimino)-5-nitro-3-hexeneamide (FK-409), (E)-alkyl-2-((E)-hydroxyimino)-5-nitro-3-hexeneamines, N-((2Z, 3E)-4-ethyl-2-(hydroxyimino)-6-methyl-5-nitro-3-heptenyl)-3-pyridinecarboxamide (FR 146801), N-nitrosoamines, N-hydroxyl nitrosamines, nitrosimines, diazetine dioxides, oxatriazole 5-imines, oximes, hydroxylamines, N-hydroxyguanidines, hydroxyureas, benzofuroxanes, furoxans as well as substrates for the endogenous enzymes which synthesize nitric oxide.

Suitable NONOates include, but are not limited to, (Z)-1-(N-methyl-N-(6-(N-methyl-ammoniohexyl)amino))diazen-1-ium-1,2-diolate ("MAHMA/NO"), (Z)-1-(N-(3-ammoniopropyl)-N-(n-propyl)amino)diazen-1-ium-1,2-diolate ("PAPA/NO"), (Z)-1-(N-(3-aminopropyl)-N-(4-(3-aminopropylammonio)butyl)-amino) diazen-1-ium-1,2-diolate (spermine NONOate or "SPER/NO") and sodium(Z)-1-(N,N-diethylamino)diazenium-1,2-diolate (diethylamine NONOate or "DEA/NO") and derivatives thereof. NONOates are also described in U.S. Patent Nos. 6,232,336, 5,910,316 and 5,650,447, the disclosures of which are incorporated herein by reference in their entirety. The "NO adducts" can be mono-nitrosylated, poly-nitrosylated, mono-nitrosated and/or poly-nitrosated at a variety of naturally susceptible or artificially provided binding sites for biologically active forms of nitrogen monoxide.

Suitable furoxanes include, but are not limited to, CAS 1609, C93-4759, C92-4678, S35b, CHF 2206, CHF 2363, and the like.

Suitable sydnonimines include, but are not limited to, molsidomine (N-ethoxycarbonyl-3-morpholinosydnonimine), SIN-1 (3-morpholinosydnonimine) CAS 936 (3-(cis-2,6-dimethylpiperidino)-N-(4-methoxybenzoyl)-sydnonimine, pirsidomine), C87-3754 (3-(cis-2,6-dimethylpiperidino)sydnonimine, linsidomine, C4144 (3-(3,3-dimethyl-1,4-thiazane-4-yl)sydnonimine hydrochloride), C89-4095 (3-(3,3-dimethyl-1,1-dioxo-1,4-thiazane-4-yl)sydnonimine hydrochloride, and the like.

Suitable oximes, include but are not limited to, NOR-1, NOR-3, NOR-4, and the like.

One group of NO adducts is the S-nitrosothiols, which are compounds that

include at least one -S-NO group. These compounds include S-nitroso-polypeptides (the term "polypeptide" includes proteins and polyamino acids that do not possess an ascertained biological function, and derivatives thereof); S-nitrosylated amino acids (including natural and synthetic amino acids and their stereoisomers and racemic mixtures and derivatives thereof); S-nitrosylated sugars; S-nitrosylated, modified and unmodified, oligonucleotides (preferably of at least 5, and more preferably 5-200 nucleotides); straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted S-nitrosylated hydrocarbons; and S-nitroso heterocyclic compounds. S-nitrosothiols and methods for preparing them are described in U.S. Patent Nos. 5,380,758 and 5,703,073; WO 97/27749; WO 98/19672; and Oae et al, *Org. Prep. Proc. Int.*, *15*(3):165-198 (1983), the disclosures of each of which are incorporated by reference herein in their entirety.

Another embodiment of the invention is S-nitroso amino acids where the nitroso group is linked to a sulfur group of a sulfur-containing amino acid or derivative thereof. Such compounds include, for example, S-nitroso-N-acetylcysteine, S-nitroso-captopril, S-nitroso-N-acetylpenicillamine, S-nitroso-homocysteine, S-nitroso-cysteine, S-nitroso-glutathione, S-nitroso-cysteinyl-glycine, and the like.

Suitable S-nitrosylated proteins include thiol-containing proteins (where the NO group is attached to one or more sulfur groups on an amino acid or amino acid derivative thereof) from various functional classes including enzymes, such as tissue-type plasminogen activator (TPA) and cathepsin B; transport proteins, such as lipoproteins; heme proteins, such as hemoglobin and serum albumin; and biologically protective proteins, such as immunoglobulins, antibodies and cytokines. Such nitrosylated proteins are described in WO 93/09806, the disclosure of which is incorporated by reference herein in its entirety. Examples include polynitrosylated albumin where one or more thiol or other nucleophilic centers in the protein are modified.

Other examples of suitable S-nitrosothiols include:

(i) $HS(C(R_e)(R_f))_mSNO$;

(ii) $ONS(C(R_e)(R_f))_mR_e$; or

(iii) $H_2N\text{-}CH(CO_2H)\text{-}(CH_2)_m\text{-}C(O)NH\text{-}CH(CH_2SNO)\text{-}C(O)NH\text{-}CH_2\text{-}CO_2H$;

wherein m is an integer from 2 to 20;

R_e and R_f are each independently a hydrogen, an alkyl, a cycloalkoxy, a halogen, a hydroxy, an hydroxyalkyl, an alkoxyalkyl, an arylheterocyclic ring, an alkylaryl, an alkylcycloalkyl, an alkylheterocyclic ring, a cycloalkylalkyl, a cycloalkylthio, an arylalklythio, an arylalklythioalkyl, an alkylthioalkyl a cycloalkenyl, an heterocyclicalkyl, an alkoxy, a haloalkoxy, an amino, an alkylamino, a dialkylamino, an arylamino, a diarylamino, an alkylarylamino, an alkoxyhaloalkyl, a sulfonic acid, a sulfonic ester, an alkylsulfonic acid, an arylsulfonic acid, an arylalkoxy, an alkylthio, an arylthio, a cyano an aminoalkyl, an aminoaryl, an aryl, an arylalkyl, an alkylaryl, a carboxamido, a alkylcarboxamido, an arylcarboxamido, an amidyl, a carboxyl, a carbamoyl, an alkylcarboxylic acid, an arylcarboxylic acid, an alkylcarbonyl, an arylcarbonyl, an ester, a carboxylic ester, an alkylcarboxylic ester, an arylcarboxylic ester, a sulfonamido, an alkylsulfonamido, an arylsulfonamido, an alkylsulfonyl, an alkylsulfonyloxy, an arylsulfonyl, arylsulphonyloxy, a sulfonic ester, an alkyl ester, an aryl ester, a urea, a phosphoryl, a nitro or K; or R_e and R_f taken together with the carbons to which they are attached form a carbonyl, a methanthial, a heterocyclic ring, a cycloalkyl group, an aryl group, an oxime, a hydrazone or a bridged cycloalkyl group;

K is $-(W_3)_a-E_b-(C(R_e)(R_f))_{p1}-E_c-(C(R_e)(R_f))_x-(W_3)_d-(C(R_e)(R_f))_y-(W_3)_i-E_j-(W_3)_g-(C(R_e)(R_f))_z-U_3-V_3$;

V_3 is –NO or $-NO_2$;

a, b, c, d, g, i and j are each independently an integer from 0 to 3;

p_1, x, y and z are each independently an integer from 0 to 10;

W_3 at each occurrence is independently -C(O)-, -C(S)-, $-T_3-$, $-(C(R_e)(R_f))_h-$, an alkyl group, an aryl group, a heterocyclic ring, an arylheterocyclic ring, or $-(CH_2CH_2O)_{q1}-$;

E at each occurrence is independently $-T_3-$, an alkyl group, an aryl group, $-(C(R_e)(R_f))_h-$, a heterocyclic ring, an arylheterocyclic ring, or $-(CH_2CH_2O)_{q1}-$;

T_3 at each occurrence is independently a covalent bond, a carbonyl, an oxygen, $-S(O)_o-$ or $-N(R_a)R_i$;

h is an integer form 1 to 10;

q_1 is an integer from 1 to 5;

U_3 at each occurrence is independently a covalent bond, a carbonyl, an oxygen, $-S(O)_o-$ or $-N(R_a)R_i$;

o is an integer from 0 to 2;

R_a is a lone pair of electrons, a hydrogen or an alkyl group;

R_i is a hydrogen, an alkyl, an aryl, an alkylcarboxylic acid, an arylcarboxylic acid, an alkylcarboxylic ester, an arylcarboxylic ester, an alkylcarboxamido, an arylcarboxamido, an alkylaryl, an alkylsulfinyl, an alkylsulfonyl, an alkylsulfonyloxy, an arylsulfinyl, an arylsulfonyl, arylsulphonyloxy, a sulfonamido, a carboxamido, a carboxylic ester, an aminoalkyl, an aminoaryl, $-CH_2-C(U_3-V_3)(R_e)(R_f)$, a bond to an adjacent atom creating a double bond to that atom, $-(N_2O_2-)^-\bullet M_1^+$, wherein M_1^+ is an organic or inorganic cation.

In cases where R_e and R_f are a heterocyclic ring or taken together R_e and R_f are a heterocyclic ring, then R_i can be a substituent on any disubstituted nitrogen contained within the radical wherein R_i is as defined herein.

In cases where R_e and R_f are a heterocyclic ring or taken together R_e and R_f are a heterocyclic ring, then R_i can be a substituent on any disubstituted nitrogen contained within the radical wherein R_i is as defined herein.

Nitrosothiols can be prepared by various methods of synthesis. In general, the thiol precursor is prepared first, then converted to the S-nitrosothiol derivative by nitrosation of the thiol group with $NaNO_2$ under acidic conditions (pH is about 2.5) which yields the S-nitroso derivative. Acids which can be used for this purpose include aqueous sulfuric, acetic and hydrochloric acids. The thiol precursor can also be nitrosylated by reaction with an organic nitrite such as tert-butyl nitrite, or a nitrosonium salt such as nitrosonium tetrafluoroborate in an inert solvent.

Another group of NO adducts for use in the invention, where the NO adduct is a compound that donates, transfers or releases nitric oxide, include compounds comprising at least one ON-O- or ON-N- group. The compounds that include at least one ON-O- or ON-N- group are preferably ON-O- or ON-N-polypeptides (the term "polypeptide" includes proteins and polyamino acids that do not possess an ascertained biological function, and derivatives thereof); ON-O- or ON-N-amino acids (including natural and synthetic amino acids and their stereoisomers and racemic mixtures);

ON-O- or ON-N-sugars; ON-O- or -ON-N- modified or unmodified oligonucleotides (comprising at least 5 nucleotides, preferably 5-200 nucleotides); ON-O- or ON-N- straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted hydrocarbons; and ON-O-, ON-N- or ON-C-heterocyclic compounds. Preferred examples of compounds comprising at least one ON-O- or ON-N- group include butyl nitrite, isobutyl nitrite, *tert*-butyl nitrite, amyl nitrite, isoamyl nitrite, N-nitrosamines, N-nitrosamides, N-nitrosourea, N-nitrosoguanidines, N-nitrosocarbamates, N-acyl-N-nitroso compounds (such as, N-methyl-N-nitrosourea); N-hydroxy-N-nitrosamines, cupferron, alanosine, dopastin, 1,3-disubstitued nitrosiminobenzimidazoles, 1,3,4-thiadiazole-2-nitrosimines, benzothiazole-2(3H)-nitrosimines, thiazole-2-nitrosimines, oligonitroso sydnonimines, 3-alkyl-N-nitroso-sydnonimines, 2H-1,3,4–thiadiazine nitrosimines.

Another group of NO adducts for use in the invention include nitrates that donate, transfer or release nitric oxide, such as compounds comprising at least one O_2N-O-, O_2N-N- or O_2N-S- group. Preferred among these compounds are O_2N-O-, O_2N-N- or O_2N-S- polypeptides (the term "polypeptide" includes proteins and also polyamino acids that do not possess an ascertained biological function, and derivatives thereof); O_2N-O-, O_2N-N- or O_2N-S- amino acids (including natural and synthetic amino acids and their stereoisomers and racemic mixtures); O_2N-O-, O_2N-N- or O_2N-S- sugars; O_2N-O-, O_2N-N– or O_2N-S- modified and unmodified oligonucleotides (comprising at least 5 nucleotides, preferably 5-200 nucleotides); O_2N-O-, O_2N-N- or O_2N-S- straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted hydrocarbons; and O_2N-O-, O_2N-N- or O_2N-S- heterocyclic compounds. Preferred examples of compounds comprising at least one O_2N-O-, O_2N-N- or O_2N-S- group include isosorbide dinitrate, isosorbide mononitrate, clonitrate, erythrityl tetranitrate, mannitol hexanitrate, nitroglycerin, pentaerythritoltetranitrate, pentrinitrol, propatylnitrate and organic nitrates with a sulfhydryl-containing amino acid such as, for example SPM 3672, SPM 5185, SPM 5186 and those disclosed in U. S. Patent Nos. 5,284,872, 5,428,061, 5,661,129, 5,807,847 and 5,883,122 and in WO 97/46521, WO 00/54756 and in WO 03/013432, the disclosures of each of which are incorporated by reference herein in their entirety.

Another group of NO adducts are N-oxo-N-nitrosoamines that donate, transfer or release nitric oxide and are represented by the formula: $R^{1"}R^{2"}N\text{-}N(O\text{-}M^{+})\text{-}NO$, where $R^{1"}$ and $R^{2"}$ are each independently a polypeptide, an amino acid, a sugar, a modified or unmodified oligonucleotide, a straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted hydrocarbon, or a heterocyclic group, and where M_1^+ is an organic or inorganic cation, such, as for example, an alkyl substituted ammonium cation or a Group I metal cation.

The invention is also directed to compounds that stimulate endogenous NO or elevate levels of endogenous endothelium-derived relaxing factor (EDRF) *in vivo* or are oxidized to produce nitric oxide and/or are substrates for nitric oxide synthase and/or cytochrome P450. Such compounds include, for example, L-arginine, L-homoarginine, and N-hydroxy-L-arginine, N-hydroxy-L-homoarginine, N-hydroxydebrisoquine, N-hydroxypentamidine including their nitrosated and/or nitrosylated analogs (e.g., nitrosated L-arginine, nitrosylated L-arginine, nitrosated N-hydroxy-L-arginine, nitrosylated N-hydroxy-L-arginine, nitrosated and nitrosylated L-homoarginine), N-hydroxyguanidine compounds, amidoxime, ketoximes, aldoxime compounds, that can be oxidized in vivo to produce nitric oxide. Compounds that may be substrates for a cytochrome P450, include, for example, imino(benzylamino)methylhydroxyl amine, imino(((4-methylphenyl)methyl) amino)methylhydroxylamine, imino(((4-methoxyphenyl)methyl)amino) methylhydroxylamine, imino(((4-(trifluoromethyl)phenyl)methyl) amino) methylhydroxylamine, imino(((4-nitrophenyl) methyl)amino)methylhydroxylamine, (butylamino) iminomethylhydroxylamine, imino (propylamino) methylhydroxylamine, imino(pentylamino)methylhydroxylamine, imino (propylamino)methylhydroxylamine, imino ((methylethyl)amino)methylhydroxylamine, (cyclopropylamino) iminomethylhydroxylamine, imino-2-1,2,3,4-tetrahydroisoquinolyl methylhydroxylamine, imino(1-methyl(2-1,2,3,4-tetrahydroisoquinolyl)) methylhydroxylamine, (1,3-dimethyl(2-1,2,3,4-tetrahydroisoquinolyl)) iminomethylhydroxylamine, (((4-chlorophenyl)methyl) amino) iminomethylhydroxylamine, ((4-chlorophenyl)amino)iminomethylhydroxylamine, (4-chlorophenyl)(hydroxyimino)methylamine, and 1-(4-chlorophenyl)-1-(hydroxyimino) ethane, and the like, precursors of L-arginine and/or physiologically acceptable salts

thereof, including, for example, citrulline, ornithine, glutamine, lysine, polypeptides comprising at least one of these amino acids, inhibitors of the enzyme arginase (e.g., N-hydroxy-L-arginine and 2(S)-amino-6-boronohexanoic acid), nitric oxide mediators and/or physiologically acceptable salts thereof, including, for example, pyruvate, pyruvate precursors, α-keto acids having four or more carbon atoms, precursors of α-keto acids having four or more carbon atoms (as disclosed in WO 03/017996, the disclosure of which is incorporated herein in its entirety), and the substrates for nitric oxide synthase, cytokines, adenosin, bradykinin, calreticulin, bisacodyl, and phenolphthalein. EDRF is a vascular relaxing factor secreted by the endothelium, and has been identified as nitric oxide (NO) or a closely related derivative thereof (Palmer et al, *Nature*, 327:524-526 (1987); Ignarro et al, *Proc. Natl. Acad. Sci. USA*, 84:9265-9269 (1987)).

The invention is also based on the discovery that compounds and compositions of the invention may be used in conjunction with other therapeutic agents for co-therapies, partially or completely, in place of other therapeutic agents, such as, for example, aldosterone antagonists, alpha-adrenergic receptor antagonists, angiotensin II antagonists, angiotensin-converting enzyme (ACE) inhibitors, antidiabetic compounds, anti-hyperlipidemic compounds, antioxidants, antithrombotic and vasodilator compounds, β-adrenergic antagonists, calcium channel blockers, digitalis, diuretics, endothelin antagonists, hydralazine compounds, H_2 receptor antagonists, neutral endopeptidase inhibitors, nonsteroidal antiinflammatory compounds (NSAIDs), phosphodiesterase inhibitors, potassium channel blockers, platelet reducing agents, proton pump inhibitors, renin inhibitors, selective cyclooxygenase-2 (COX-2) inhibitors, and combinations of two or more thereof. The therapeutic agent may optionally be nitrosated and/or nitrosylated.

Suitable aldosterone antagonists include, but are not limited to, canrenone, potassium canrenoate, drospirenone, spironolactone, eplerenone (INSPRA®), epoxymexrenone, fadrozole, pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo, γ-lactone, methyl ester, (7α,11α,17β.)-; pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo-dimethyl ester, (7α,11α,17β.)-; 3'H-cyclopropa(6,7)pregna-4,6-diene-21-carboxylic acid, 9,11-epoxy-6,7-dihydro-17-

hydroxy-3-oxo-, γ-lactone, (6β,7β,11α,17β)-; pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo-, 7-(1-methylethyl) ester, monopotassium salt, (7α,11α,17β.)-; pregn-4-ene-7,21-dicarboxylic acid, 9,11,-epoxy-17-hydroxy-3-oxo-, 7-methyl ester, monopotassium salt, (7α,11α,17β.)-; 3'H-cyclopropa(6,7) pregna-1,4,6-triene-21-carboxylic acid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-, γ-lactone, (6β,7β,11α)-; 3'H-cyclopropa(6,7)pregna-4,6-diene-21-carboxylic acid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-, methyl ester, (6β,7β,11α,17β)-; 3'H-cyclopropa (6,7)pregna-4,6-diene-21-carboxylic acid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-, monopotassium salt, (6β,7β,11α,17β)-; 3'H-cyclopropa(6,7)pregna-1,4,6-triene-21-carboxylic acid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-, γ-lactone, (6β,7β,11α,17β)-; pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo-, γ-lactone, ethyl ester, (7α,11α,17β)-; pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo-, γ-lactone, 1-methylethyl ester, (7α,11α,17β)-; RU-28318, and the like. Suitable aldosterone antagonists are described more fully in the literature, such as in Goodman and Gilman, The Pharmacological Basis of Therapeutics (9th Edition), McGraw-Hill, 1995; and the Merck Index on CD-ROM, 13th Edition; and on STN Express, file phar and file registry.

In some embodiment the aldosterone antagonists is eplerenone or spironolactone (a potassium sparing diuretic that acts like an aldosterone antagonist). In more particular embodiments eplerenone is administered in an amount of about 25 milligrams to about 300 milligrams as a single dose or as multiple doses per day; the spironolactone is administered in an amount of about 25 milligrams to about 150 milligrams as a single dose or as multiple doses per day.

Suitable alpha-adrenergic receptor antagonists include but are not limited to, phentolamine, tolazoline, idazoxan, deriglidole, RX 821002, BRL 44408, BRL 44409, BAM 1303, labetelol, ifenprodil, rauwolscine, corynathine, raubascine, tetrahydroalstonine, apoyohimbine, akuammigine, β-yohimbine, yohimbol, yohimbine, pseudoyohimbine, epi-3α-yohimbine, 10-hydroxy-yohimbine, 11-hydroxy-yohimbine, tamsulosin, benoxathian, atipamezole, BE 2254, WB 4101, HU-723, tedisamil, mirtazipine, setiptiline, reboxitine, delequamine, naftopil, saterinone, SL 89.0591, ARC 239, urapidil, 5-methylurapidil, monatepi, haloperidol, indoramin, SB 216469,

moxisylyte, trazodone, dapiprozole, efaroxan, Recordati 15/2739, SNAP 1069, SNAP 5089, SNAP 5272, RS 17053, SL 89.0591, KMD 3213, spiperone, AH 11110A, chloroethylclonidine, BMY 7378, niguldipine, and the like. Suitable alpha-adrenergic receptor antagonists are described more fully in the literature, such as in Goodman and Gilman, The Pharmacological Basis of Therapeutics (9th Edition), McGraw-Hill, 1995; and the Merck Index on CD-ROM, Thirteenth Edition; and on STN Express, file phar and file registry.

Suitable angiotensin II antagonists include, but are not limited to, angiotensin, abitesartan, candesartan, candesartan cilexetil, elisartan, embusartan, enoltasosartan, eprosartan, fonsartan, forasartan, glycyllosartan, irbesartan, losartan, olmesartan, milfasartan, medoxomil, riposartan, pratosartan, saprisartan, saralasin, sarmesin, tasosartan, telmisartan, valsartan, zolasartin, 3-(2'(tetrazole-5-yl)-1,1'-biphen-4-yl)methyl-5,7-dimethyl-2-ethyl-3H-imidazo(4,5-b)pyridine, antibodies to angiotensin II, A-81282, A-81988, BAY-106734, BIBR-363, BIBS-39, BIBS-222, BMS-180560, BMS-184698, BMS-346567, CGP-38560A, CGP-42112A, CGP-48369, CGP-49870, CGP-63170, CI-996, CP-148130, CL-329167, CV-11194, DA-2079, DE-3489, DMP-811, DuP-167, DuP-532, DuP-753, E-1477, E-4177, E-4188, EMD-66397, EMD-73495, EMD-66684, EXP-063, EXP-929, EXP-3174, EXP-6155, EXP-6803, EXP-7711, EXP-9270, EXP-9954, FK-739, FR-1153332, GA-0050, GA-0056, HN-65021, HOE-720, HR-720, ICI-D6888, ICI-D7155, ICI-D8731, KRI-1177, KT3-671, KT-3579, KW-3433, L-158809, L-158978, , L-159282, L-159689, L-159874, L-161177, L-162154, L-162234, L-162441, L-163007, L-163017, LF-70156, LR B087, LRB-057, LRB-081, LY-235656, LY-266099, LY-285434, LY-301875, LY-302289, LY-315995, ME-3221, MK-954, PD-123177, PD-123319, PD-126055, PD-150304, RG-13647, RWJ-38970, RWJ-46458, S-8307, S-8308, SC-51757, SC-54629, SC-52458, SK 1080, SL-910102, TAK-536, UP-2696, U-96849, U-97018, UK-77778, UP-275-22, WAY-126227, WK-1260, WK-1360, WK-1492, WY 126227, YH-1498, YM-358, YM-31472, X-6803, XH-148, XR-510, ZD-6888, ZD-7155, ZD-8731, ZD 8131, the compounds of ACS registry numbers 124750-92-1, 133240-46-7, 135070-05-2, 139958-16-0, 145160-84-5, 147403-03-0, 153806-29-2, 439904-54-8P, 439904-55-9P, 439904-56-0P, 439904-57-1P, 439904-58-2P, 155918-60-8P, 155918-61-9P, 272438-

16-1P, 272446-75-0P, 223926-77-0P, 169281-89-4, 439904-65-1P, 165113-01-9P, 165113-02-0P, 165113-03-1P, 165113-03-2P, 165113-05-3P, 165113-06-4P, 165113-07-5P, 165113-08-6P, 165113-09-7P, 165113-10-0P, 165113-11-1P, 165113-12-2P, 165113-17-7P, 165113-18-8P, 165113-19-9P, 165113-20-2P, 165113-13-3P, 165113-14-4P, 165113-15-5P, 165113-16-6P, 165113-21-3P, 165113-22-4P, 165113-23-5P, 165113-24-6P, 165113-25-7P, 165113-26-8P, 165113-27-9P, 165113-28-0P, 165113-29-1P, 165113-30-4P, 165113-31-5P, 165113-32-6P, 165113-33-7P, 165113-34-8P, 165113-35-9P, 165113-36-0P, 165113-37-1P, 165113-38-2P, 165113-39-3P, 165113-40-6P, 165113-41-7P, 165113-42-8P, 165113-43-9P, 165113-44-0P, 165113-45-1P, 165113-46-2P, 165113-47-3P, 165113-48-4P, 165113-49-5P, 165113-50-8P, 165113-51-9P, 165113-52-0P, 165113-53-1P, 165113-54-2P, 165113-55-3P, 165113-56-4P, 165113-57-5P, 165113-58-6P, 165113-59-7P, 165113-60-0P, 165113-61-1P, 165113-62-2P, 165113-63-3P, 165113-64-4P, 165113-65-5P, 165113-66-6P, 165113-67-7P, 165113-68-8P, 165113-69-9P, 165113-70-2P, 165113-71-3P, 165113-72-4P, 165113-73-5P, 165113-74-6P, 114798-27-5, 114798-28-6, 114798-29-7, 124749-82-2, 114798-28-6, 124749-84-4, 124750-88-5, 124750-91-0,124750-93-2, 161946-65-2P, 161947-47-3P, 161947-48-4P, 161947-51-9P, 161947-52-0P, 161947-55-3P, 161947-56-4P, 161947-60-0P, 161947-61-1P, 161947-68-8P, 161947-69-9P, 161947-70-2P, 161947-71-3P, 161947-72-4P, 161947-74-6P, 161947-75-7P, 161947-81-5P, 161947-82-6P, 161947-83-7P, 161947-84-8P, 161947-85-9P, 161947-86-0P, 161947-87-1P, 161947-88-2P, 161947-89-3P, 161947-90-6P, 161947-91-7P, 161947-92-8P, 161947-93-9P, 161947-94-0P, 161947-95-1P, 161947-96-2P, 161947-97-3P, 161947-98-4P, 161947-99-5P, 161948-00-1P, 161948-01-2P, 161948-02-3P, 168686-32-6P, 167301-42-0P, 166813-82-7P, 166961-56-4P, 166961-58-6P, 158872-96-9P, 158872-97-0P, 158807-14-8P, 158807-15-9P, 158807-16-0P, 158807-17-1P, 158807-18-2P, 158807-19-3P, 158807-20-6P, 155884-08-5P, 154749-99-2, 167371-59-7P, 244126-99-6P, 177848-35-0P and 141309-82-2P, and the like. Suitable angiotensin II antagonists are described more fully in the literature, such as in Goodman and Gilman, The Pharmacological Basis of Therapeutics (9th Edition), McGraw-Hill, 1995; and the Merck Index on CD-ROM, 13th Edition; and on STN Express, file phar and file registry.

In some embodiments the angiotensin II antagonists are candesartan, eprosartan,

irbesartan, losartan, omlesartan, telmisartan or valsartan. In more particular embodiments the candesartan is administered as candesartan cilexetil in an amount of about 15 milligrams to about 100 milligrams as a single dose or as multiple doses per day; the eprosartan, is administered as eprosartan mesylate in an amount of about 400 milligrams to about 1600 milligrams as a single does or as multiple doses per day; the irbesartan is administered in an amount of about 75 milligrams to about 1200 milligrams as a single dose or as multiple doses per day; the losartan is administered as losartan potassium in an amount of about 25 milligrams to about 100 milligrams as a single dose or as multiple doses per day; the omlesartan is administered as omlesartan medoxomil in an amount of about 5 milligrams to about 40 milligrams as a single dose or as multiple doses per day; the telmisartan is administered in an amount of about 20 milligrams to about 80 milligrams as a single dose or as multiple doses per day; the valsartan is administered in an amount of about 80 milligrams to about 320 milligrams as a single dose or as multiple doses per day.

Suitable angiotensin-converting enzyme inhibitors (ACE inhibitors) include, but are not limited to, alacepril, benazepril (LOTENSIN®, CIBACEN®), benazeprilat, captopril, ceronapril, cilazapril, delapril, duinapril, enalapril, enalaprilat, fasidotril, fosinopril, fosinoprilat, gemopatrilat, glycopril, idrapril, imidapril, lisinopril, moexipril, moveltipril, naphthopidil, omapatrilat, pentopril, perindopril, perindoprilat, quinapril, quinaprilat, ramipril, ramiprilat, rentipril, saralasin acetate, spirapril, temocapril, trandolapril, trandolaprilat, urapidil, zofenopril, acylmercapto and mercaptoalkanoyl pralines, carboxyalkyl dipeptides, carboxyalkyl dipeptide, phosphinylalkanoyl pralines, registry no.796406, AVE 7688, BP1.137, CHF 1514, E 4030, ER 3295, FPL-66564, MDL 100240, RL 6134, RL 6207, RL 6893, SA 760, S-5590, Z 13752A, and the like. Suitable angiotensin-converting enzyme inhibitors are described more fully in the literature, such as in Goodman and Gilman, The Pharmacological Basis of Therapeutics (9th Edition), McGraw-Hill, 1995; and the Merck Index on CD-ROM, Twelfth Edition, Version 12:1, 1996; and on STN Express, file phar and file registry.

In some embodiments the angiotensin-converting enzyme inhibitors are benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, quinapril, ramipril, trandolapril or trandolaprilat. In more particular embodiments the benazepril is

administered as benazepril hydrochloride in an amount of about 5 milligrams to about 80 milligrams as a single dose or as multiple doses per day; the captopril is administered in an amount of about 12.5 milligrams to about 450 milligrams as a single does or as multiple doses per day; the enalapril is administered as enalapril maleate in an amount of about 2.5 milligrams to about 40 milligrams as a single dose or as multiple doses per day; the fosinopril is administered as fosinopril sodium in an amount of about 5 milligrams to about 60 milligrams as a single dose or as multiple doses per day; the lisinopril is administered in an amount of about 12.5 milligrams to about 75 milligrams as a single dose or as multiple doses per day; the moexipril is administered as moexipril hydrochloride in an amount of about 7.5 milligrams to about 45 milligrams as a single dose or as multiple doses per day; the quinapril is administered as quinapril hydrochloride in an amount of about 5 milligrams to about 40 milligrams as single or multiple doses per day; the ramapril hydrochloride in an amount of about 1.25 milligrams to about 40 milligrams as single or multiple doses per day; the trandolapril is administered as in an amount of about 0.5 milligrams to about 4 milligrams as single or multiple doses per day; the trandolaprilat is administered as in an amount of about 0.5 milligrams to about 4 milligrams as single or multiple doses per day.

Suitable antidiabetic compounds include but are not limited to, acarbose, acetohexamide, buformin, carbutamide, chlorpropamide, glibornuride, gliclazide, glimepiride, glipizide, gliquidone, glisoxepid, glyburide, glybuthiazol(e), glybuzole, glyhexamide, glymidine, glypinamide, insulin, metformin, miglitol, nateglinide, phenbutamide, phenformin, pioglitazone, repaglinide, rosiglitazone, tolazamide, tolbutamide, tolcyclamide, troglitazone, voglibose, and the like. Suitable antidiabetic compounds are described more fully in the literature, such as in Goodman and Gilman, The Pharmacological Basis of Therapeutics (9th Edition), McGraw-Hill, 1995; and the Merck Index on CD-ROM, Thirteenth Edition; and on STN Express, file phar and file registry.

Suitable anti-hyperlipidemic compounds include, but are not limited to, statins or HMG-CoA reductase inhibitors, such as, for example, atorvastatin (LIPITOR®), bervastatin, cerivastatin (BAYCOL®), dalvastatin, fluindostatin (Sandoz XU-62-320),

fluvastatin, glenvastatin, lovastatin (MEVACOR®), mevastatin, pravastatin (PRAVACHOL®), rosuvastatin (CRESTRO®), simvastatin (ZOCOR®), velostatin (also known as synvinolin), VYTORIN™ (ezetimibe/simvastatin), GR-95030, SQ 33,600, BMY 22089, BMY 22,566, CI 980, and the like; gemfibrozil, cholystyramine, colestipol, niacin, nicotinic acid, bile acid sequestrants, such as, for example, cholestyramine, colesevelam, colestipol, poly(methyl-(3-trimethylaminopropyl) imino-trimethylene dihalide) and the like; probucol; fibric acid agents or fibrates, such as, for example, bezafibrate (Bezalip™), beclobrate, binifibrate, ciprofibrate, clinofibrate, clofibrate, etofibrate, fenofibrate (Lipidil™, Lipidil Micro™), gemfibrozil (Lopid™.), nicofibrate, pirifibrate, ronifibrate, simfibrate, theofibrate and the like; cholesterol ester transfer protein (CETP) inhibitors, such as for example, CGS 25159, CP-529414 (torcetrapid), JTT-705, substituted N-[3-(1,1,2,2-tetrafluoroethoxy)benzyl]-N-(3-phenoxyphenyl)-trifluoro-3-amino-2-propanols, N,N-disubstituted trifluoro-3-amino-2-propanols, PD 140195 (4-phenyl-5-tridecyl-4H-1,2,4- triazole-3-thiol), SC-794, SC-795, SCH 58149, and the like.

In some embodiments the anti-hyperlipidemic compounds are atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin or simvastatin. In more particular embodiments the atorvastatin is administered in an amount of about 10 milligrams to about 80 milligrams as a single dose or as multiple doses per day; the fluvastatin is administered in an amount of about 20 milligrams to about 80 milligrams as a single does or as multiple doses per day; the lovastatin is administered in an amount of about 10 milligrams to about 80 milligrams as a single dose or as multiple doses per day; the pravastatin is administered in an amount of about 10 milligrams to about 80 milligrams as a single dose or as multiple doses per day; the rosuvastatin is administered in an amount of about 5 milligrams to about 40 milligrams as a single dose or as multiple doses per day; the simvastatin is administered in an amount of about 5 milligrams to about 80 milligrams as a single dose or as multiple doses per day.

Suitable antioxidants include, but are not limited to, small-molecule antioxidants and antioxidant enzymes. Suitable small-molecule antioxidants include, but are not limited to, hydralazine compounds, glutathione, vitamin C, vitamin E, cysteine, N-acetyl-cysteine, β-carotene, ubiquinone, ubiquinol-10, tocopherols,

coenzyme Q, superoxide dismutase mimetics, such as, for example, 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), DOXYL, PROXYL nitroxide compounds; 4-hydroxy-2,2,6,6-tetramethyl-1-piperidinyloxy (Tempol), M-40401, M-40403, M-40407, M-40419,M-40484, M-40587, M-40588, and the like. Suitable antioxidant enzymes include, but are not limited to, superoxide dismutase, catalase, glutathione peroxidase, NADPH oxidase inhibitors, such as, for example, apocynin, aminoguanidine, ONO 1714, S17834 (benzo(b)pyran-4-one derivative), and the like; xanthine oxidase inhibitors, such as, for example, allopurinol, oxypurinol, amflutizole, diethyldithiocarbamate, 2-styrylchromones, chrysin, luteolin, kaempferol, quercetin, myricetin, isorhamnetin, benzophenones such as 2,2',4,4'-tetrahydroxybenzophenone, 3,4,5,2',3',4'-hexahydroxybenzophenone and 4,4'-dihydroxybenzophenone; benzothiazinone analogues such as 2-amino-4H-1,3-benzothiazine-4-one, 2-guanidino-4H-1,3-benzothiazin-4-one and rhodanine; N-hydroxyguanidine derivative such as, PR5 (1-(3, 4-dimethoxy-2-chlorobenzylideneamino)-3-hydroxyguanidine); 6-formylpterin, and the like. The antioxidant enzymes can be delivered by gene therapy as a viral vertor and/or a non-viral vector. Suitable antioxidants are described more fully in the literature, such as in Goodman and Gilman, The Pharmacological Basis of Therapeutics (9th Edition), McGraw-Hill, 1995; and the Merck Index on CD-ROM, Thirteenth Edition; and on STN Express, file phar and file registry.

In some embodiments the antioxidants are apocynin, hydralazine compounds and superoxide dimutase mimetics.

Suitable antithrombotic and vasodilator compounds include, but are not limited to, abciximab, acetorphan, acetylsalicylic acid, argatroban, bamethan, benfurodil, benziodarone, betahistine, bisaramil, brovincamine, bufeniode, citicoline, clobenfurol, clopidogrel, cyclandelate, dalteparin, dipyridamol, droprenilamine, enoxaparin, fendiline, ifenprodil, iloprost, indobufen, isobogrel, isoxsuprine, heparin, lamifiban, midrodine, nadroparin, nicotinoyl alcohol, nylidrin, ozagrel, perhexiline, phenylpropanolamine, prenylamine, papaveroline, reviparin sodium salt, ridogrel, suloctidil, tinofedrine, tinzaparin, trifusal, vintoperol, xanthinal niacinate, and the like. Suitable antithrombotic and vasodilator compounds are described more fully in the literature, such as in Goodman and Gilman, The Pharmacological Basis of Therapeutics

(9th Edition), McGraw–Hill, 1995; and the Merck Index on CD-ROM, Thirteenth Edition; and on STN Express, file phar and file registry.

Suitable β-adrenergic antagonists include, but are not limited to, acebutolol, alprenolol, amosulalol, arotinolol, atenolol, befunolol, betaxolol, bevantolol, bisoprolol, bopindolol, bucindolol, bucumolol, bufetolol, bufuralol, bunitrolol, bupranolol, butofilolol, carazolol, capsinolol, carteolol, carvedilol (COREG®), celiprolol, cetamolol, cindolol, cloranolol, dilevalol, diprafenone, epanolol, ersentilide, esmolol, esprolol, hedroxalol, indenolol, labetalol, landiolol, laniolol, levobunolol, mepindolol, methylpranol, metindol, metipranolol, metrizoranolol, metoprolol, moprolol, nadolol, nadoxolol, nebivolol, nifenalol, nipradilol, oxprenolol, penbutolol, pindolol, practolol, pronethalol, propranolol, sotalol, sotalolnadolol, sulfinalol, taliprolol, talinolol, tertatolol, tilisolol, timolol, toliprolol, tomalolol, trimepranol, xamoterol, xibenolol, 2-(3-(1,1-dimethylethyl)-amino-2-hydroxypropoxy)-3-pyridenecarbonitrilHCl, 1-butylamino-3-(2,5-dichlorophenoxy)-2-propanol, 1-isopropylamino-3-(4-(2-cyclopropylmethoxyethyl) phenoxy)-2-propanol, 3-isopropylamino-1-(7-methylindan-4-yloxy)-2-butanol, 2-(3-t-butylamino-2-hydroxy-propylthio)-4-(5-carbamoyl-2-thienyl)thiazol, 7-(2-hydroxy-3-t-butylaminpropoxy)phthalide, Acc 9369, AMO-140, BIB-16S, CP-331684, Fr-172516, ISV-208, L-653328, LM-2616, SB-226552, SR-58894A, SR-59230A, TZC-5665, UK-1745, YM-430, and the like. Suitable β-adrenergic antagonists are described more fully in the literature, such as in Goodman and Gilman, The Pharmacological Basis of Therapeutics (9th Edition), McGraw-Hill, 1995; and the Merck Index on CD-ROM, 13th Edition; and on STN Express, file phar and file registry.

In some embodiments the β-adrenergic antagonists are atenolol, bisoprolol, carvedilol, metoprolol, nebivolol, propranolol or timolol. In more particular embodiments the atenolol is administered in an amount of about 50 milligrams to about 200 milligrams as a single dose or as multiple doses per day; the bisoprolol is administered as bisoprolol fumarate in an amount of about 2.5 milligrams to about 30 milligrams as a single dose or as multiple doses per day; the carvedilol is administered in an amount of about 3.125 milligrams to about 200 milligrams as a single does or as multiple doses per day; the metoprolol is administered as metoprolol tartarate in an

amount of about 50 milligrams to about 300 milligrams as a single dose or as multiple doses per day; the nebivolol is administered as nebivolol hydrochloride in an amount of about 2.5 milligrams to about 20 milligrams as a single dose or as multiple doses per day; the propranolol is administered as propranolol hydrochloride in an amount of about 40 milligrams to about 240 milligrams as a single dose or as multiple doses per day; the timolol is administered as timolol maleate in an amount of about 10 milligrams to about 30 milligrams as a single dose or as multiple doses per day.

Suitable calcium channel blockers include, but are not limited to, amlodipine (NORVASC®), anipamil, aranidipine, amrinone, azelnidipine, barnidipine, bencyclane, benidipine, bepridil, cilnidipine, cinnarizine, clentiazem, diltiazem, dotarizine, efonidipine, elgodipine, fantofarone, felodipine, fendiline, flunarizine, fluspirilene, furnidipine, gallopamil, ipenoxazone, isradipine, lacidipine, lemildipine, lercanidipine, lomerizine, manidipine, mibefradil, monatepil, nicardipine, nifedipine, niguldipine, niludipine, nilvadipine, nimodipine, nisoldipine, nitrendipine, nivaldipine, oxodipine, perhexilene, phenytoin, phenytprenylamine, pranidipine, ranolazine, ryosidine, semotiadil, tamolarizine, temiverine hydrochloride, terodiline, tiapamil, vatanidipine hydrochloride, verapamil, ziconotide, AE-0047, CAI, JTV-519, CHF-1521, L-651582, NS-7, NW-1015, RO-2933, SB-237376, SL-34.0829-08, S-312d, SD-3212, TA-993, YM-430, and the like. Suitable calcium channel blockers are described more fully in the literature, such as in Goodman and Gilman, The Pharmacological Basis of Therapeutics (9th Edition), McGraw-Hill, 1995; and the Merck Index on CD-ROM, Thirteenth Edition; and on STN Express, file phar and file registry.

In some embodiments the calcium channel blockers are amlodipine, diltiazem, isradipine, nicardipine, nifedipine, nimodipine, nisoldipine, nitrendipine, verapamil.

Suitable digitals include but are not limited to digoxin and digoxitin. In some embodiments the digoxin is administered to achieve a steady state blood serum concentration of at least about 0.7 nanograms per ml to about 2.0 nanograms per ml.

Suitable diuretics include but are not limited to, thiazides (such as, for example, althiazide, bendroflumethiazide, benzclortriazide, benzhydrochlorothiazide,

benzthiazide, buthiazide, chlorothiazide, cyclopenethiazide, cyclothiazide, epithiazide, ethiazide, hydrobenzthiazide, hydrochlorothiazide, hydroflumethiazide, methylclothiazide, methylcyclothiazide, penflutazide, polythiazide, teclothiazide, trichlormethiazide, triflumethazide, and the like); alilusem, ambuside, amiloride, aminometradine, azosemide, bemetizide, bumetanide, butazolamide, butizide, canrenone, carperitide, chloraminophenamide, chlorazanil, chlormerodrin, chlorthalidone, cicletanide, clofenamide, clopamide, clorexolone, conivaptan, daglutril, dichlorophenamide, disulfamide, ethacrynic acid, ethoxzolamide, etozolon, fenoldopam, fenquizone, furosemide, indapamide, mebutizide, mefruside, meralluride, mercaptomerin sodium, mercumallylic acid, mersalyl, methazolamide, meticane, metolazone, mozavaptan, muzolimine, N-(5-1,3,4-thiadiazol-2-yl)acetamide, nesiritide, pamabrom, paraflutizide, piretanide, protheobromine, quinethazone, scoparius, spironolactone, theobromine, ticrynafen, torsemide, torvaptan, triamterene, tripamide, ularitide, xipamide or potassium, AT 189000, AY 31906, BG 9928, BG 9791, C 2921, DTI 0017, JDL 961, KW 3902, MCC 134, SLV 306, SR 121463, WAY 140288, ZP 120, and the like. Suitable diuretics are described more fully in the literature, such as in Goodman and Gilman, The Pharmacological Basis of Therapeutics (9th Edition), McGraw-Hill, 1995; and the Merck Index on CD-ROM, 13th Edition; and on STN Express, file phar and file registry.

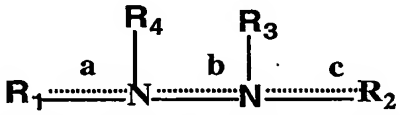
Depending on the diuretic employed, potassium may also be administered to the patient in order to optimize the fluid balance while avoiding hypokalemic alkalosis. The administration of potassium can be in the form of potassium chloride or by the daily ingestion of foods with high potassium content such as, for example, bananas or orange juice. The method of administration of these compounds is described in further detail in U.S. Patent No. 4,868,179, the disclosure of which is incorporated by reference herein in its entirety.

In some embodiments the diuretics are amiloride, furosemide, chlorthalidone, hydrochlorothiazide or triamterene. In more particular embodiments the amiloride is administered as amiloride hydrochloride in an amount of about 5 milligrams to about 15 milligrams as a single dose or as multiple doses per day; the furosemide is administered in an amount of about 10 milligrams to about 600 milligrams as a single

does or as multiple doses per day; the chlorthalidone is administered in an amount of about 15 milligrams to about 150 milligrams as a single dose or as multiple doses per day; the hydrochlorothiazide is administered in an amount of about 12.5 milligrams to about 300 milligrams as a single dose or as multiple doses per day; the triamterene is administered in an amount of about 35 milligrams to about 225 milligrams as a single dose or as multiple doses per day.

Suitable endothelin antagonists include, but are not limited to, atrasentan, bosentan, darusentan, endothelin, enrasentan, sitaxsentan, sulfonamide endothelin antagonists, tezosentan, BMS 193884, BQ-123, SQ 28608, and the like. Suitable endothelin antagonists are described more fully in the literature, such as in Goodman and Gilman, The Pharmacological Basis of Therapeutics (9th Edition), McGraw-Hill, 1995; and the Merck Index on CD-ROM, Thirteenth Edition; and on STN Express, file phar and file registry.

Suitable hydralazine compounds include, but are not limited to, compounds having the formula:



wherein a, b and c are independently a single or double bond; R_1 and R_2 are each independently a hydrogen, an alkyl, an ester or a heterocyclic ring, wherein alkyl, ester and heterocyclic rind are as defined herein; R_3 and R_4 are each independently a lone pair of electrons or a hydrogen, with the proviso that at least one of R_1, R_2, R_3 and R_4 is not a hydrogen. Exemplary hydralazine compounds include budralazine, cadralazine, dihydralazine, endralazine, hydralazine, pildralazine, todralazine, and the like. Suitable hydralazine compounds are described more fully in the literature, such as in Goodman and Gilman, The Pharmacological Basis of Therapeutics (9th Edition), McGraw-Hill, 1995; and the Merck Index on CD-ROM, Thirteenth Edition; and on STN Express, file phar and file registry.

In some embodiments the hydralazine compound is hydralazine or a pharmaceutically acceptable salt thereof such as hydralazine hydrochloride. In more particular embodiments the hydralazine is administered as hydralazine hydrochloride in an amount of about 10 milligrams to about 300 milligrams as a single dose or as

multiple doses per day.

Suitable H_2 receptor antagonists include, but are not limited to, burimamide, cimetidine, ebrotidin, famotidine, nizatidine, roxatidine, rantidine, tiotidine, and the like. Suitable H_2 receptor antagonists are described more fully in the literature, such as in Goodman and Gilman, The Pharmacological Basis of Therapeutics (9th Edition), McGraw-Hill, 1995, Pgs. 901-915; the Merck Index on CD-ROM, 13th Edition; and in WO 00/28988 assigned to NitroMed Inc., the disclosures of which are incorporated herein by reference in their entirety.

Suitable neutral endopeptidase inhibitors include, but are not limited to, atrial natriuretic peptides, diazapins, azepinones, ecadotril, fasidotril, fasidotrilat, omapatrilat, sampatrilat, BMS 189,921, Z 13752 A, and the like. Neutral endopeptidase inhibitors are described more fully in the literature, such as in Goodman and Gilman, The Pharmacological Basis of Therapeutics (9th Edition), McGraw-Hill, 1995; and the Merck Index on CD-ROM, Thirteenth Edition; and on STN Express, file phar and file registry.

Suitable NSAIDs include, but are not limited to, acetaminophen, acemetacin, aceclofenac, alminoprofen, amfenac, bendazac, benoxaprofen, bromfenac, bucloxic acid, butibufen, carprofen, cinmetacin, clopirac, diclofenac, etodolac, felbinac, fenclozic acid, fenbufen, fenoprofen, fentiazac, flunoxaprofen, flurbiprofen, ibufenac, ibuprofen, indomethacin, isofezolac, isoxepac, indoprofen, ketoprofen, lonazolac, loxoprofen, metiazinic acid, mofezolac, miroprofen, naproxen, oxaprozin, pirozolac, pirprofen, pranoprofen, protizinic acid, salicylamide, sulindac, suprofen, suxibuzone, tiaprofenic acid, tolmetin, xenbucin, ximoprofen, zaltoprofen, zomepirac, aspirin, acemetcin, bumadizon, carprofenac, clidanac, diflunisal, enfenamic acid, fendosal, flufenamic acid, flunixin, gentisic acid, ketorolac, meclofenamic acid, mefenamic acid, mesalamine, prodrugs thereof, and the like. Suitable NSAIDs are described more fully in the literature, such as in Goodman and Gilman, The Pharmacological Basis of Therapeutics (9th Edition), McGraw-Hill, 1995, Pgs. 617-657; the Merck Index on CD-ROM, 13th Edition; and in U.S. Patent Nos. 6,057,347 and 6,297,260 assigned to NitroMed Inc., the disclosures of which are incorporated herein by reference in their entirety.

In some embodiments the NSAIDs are acetaminophen, diclofenac, flurbiprofen, ibuprofen, indomethacin, ketoprofen, naproxen or aspirin. In more particular embodiments the acetaminophen is administered in an amount of about 325 milligrams to about 4 grams as a single dose or as multiple doses per day; the diclofenac is administered in an amount of about 50 milligrams to about 250 milligrams as a single does or as multiple doses per day; the flurbiprofen is administered in an amount of about 100 milligrams to about 300 milligrams as a single does or as multiple doses per day; the ibuprofen is administered in an amount of about 400 milligrams to about 3.2 grams as a single does or as multiple doses per day; the indomethacin is administered in an amount of about 25 milligrams to about 200 milligrams as a single does or as multiple doses per day; the ketoprofen is administered in an amount of about 50 milligrams to about 300 milligrams as a single does or as multiple doses per day; the naproxen is administered in an amount of about 250 milligrams to about 1.5 grams as a single does or as multiple doses per day; the aspirin is administered in an amount of about 10 milligrams to about 2 grams as a single does or as multiple doses per day.

Suitable phosphodiesterase inhibitors, include but are not limited to, filaminast, piclamilast, rolipram, Org 20241, MCI-154, roflumilast, toborinone, posicar, lixazinone, zaprinast, sildenafil, pyrazolopyrimidinones, motapizone, pimobendan, zardaverine, siguazodan, CI 930, EMD 53998, imazodan, saterinone, loprinone hydrochloride, 3-pyridinecarbonitrile derivatives, acefylline, albifylline, bamifylline, denbufyllene, diphylline, doxofylline, etofylline, torbafylline, theophylline, nanterinone, pentoxofylline, proxyphylline, cilostazol, cilostamide, MS 857, piroximone, milrinone, amrinone, tolafentrine, dipyridamole, papaveroline, E4021, thienopyrimidine derivatives, triflusal, ICOS-351, tetrahydropiperazino(1,2-b)beta-carboline-1,4-dione derivatives, carboline derivatives, 2-pyrazolin-5-one derivatives, fused pyridazine derivatives, quinazoline derivatives, anthranilic acid derivatives, imidazoquinazoline derivatives, tadalafil, vardenafil, and in Goodman and Gilman, The Pharmacological Basis of Therapeutics (9th Ed.), McGraw-Hill, Inc. (1995), The Physician's Desk Reference (49th Ed.), Medical Economics (1995), Drug Facts and Comparisons (1993 Ed), Facts and Comparisons (1993), and the Merck Index on CD-ROM, 13th Edition; and the like. Phosphodiesterase inhibitors and their nitrosated and/or nitrosylated

derivatives are also disclosed in U. S. Patent Nos. 5,932,538, 5,994,294, 5,874,437, 5,958,926 reissued as U. S. Patent No. RE 03772346,172,060, 6,197,778, 6,177,428, 6,172,068, 6,221,881, 6,232,321, 6,197,782, 6,133,272, 6,211,179, 6,316,457 and 6,331,542, the disclosures of each of which are incorporated herein by reference in their entirety.

Suitable potassium channel blockers include but are not limited to, nicorandil, pinacidil, cromakalim (BRL 34915), aprikalim, bimakalim, emakalim, lemakalim, minoxidil, diazoxide, 9-chloro-7-(2-chlorophenyl)-5H-pyrimido(5,4,-d)(2)-benzazepine, Ribi, CPG-11952, CGS-9896, ZD 6169, diazixide, Bay X 9227, P1075, Bay X 9228, SDZ PCO 400, WAY-120,491, WAY-120,129, Ro 31-6930, SR 44869, BRL 38226, S 0121, SR 46142A, CGP 42500, SR 44994, artilide fumarate, lorazepam, temazepam, rilmazafone, nimetazepam, midazolam, lormetazepam, loprazolam, ibutilide fumarate, haloxazolam, flunitrazepam, estazolam, doxefazepam, clonazepam, cinolazepam, brotizolam, and the like. Suitable potassium channel blockers are described more fully in the literature, such as in Goodman and Gilman, The Pharmacological Basis of Therapeutics (9th Edition), McGraw-Hill, 1995; and the Merck Index on CD-ROM, Thirteenth Edition; and on STN Express, file phar and file registry.

Suitable platelet reducing agents include but are not limited to, fibrinolytic agents such as for example, ancrod, anistreplase, bisobrin lactate, brinolase, Hageman factor (i.e. factor XII) fragments, plasminogen activators such as, for example, streptokinase, tissue plasminogen activators (TPA), urokinase, pro-urokinase, recombinant TPA, plasmin, plasminogen, and the like; anti-coagulant agents including but are not limited to, inhibitors of factor Xa, factor TFPI, factor VIIa, factor IXc, factor Va, factor VIIIa, inhibitors of other coagulation factors, and the like; vitamin K antagonists, such as, for example, coumarin, coumarin derivatives (e.g., warfarin sodium); glycosoaminoglycans such as, for example, heparins both in unfractionated form and in low molecular weight form; ardeparin sodium, bivalirudin, bromindione, coumarin, dalteparin sodium, danaparoid sodium; dazoxiben hydrochloride, desirudin, dicumarol, efegatran sulfate, enoxaparin sodium, ifetroban, ifetroban sodium, lyapolate sodium, nafamostat mesylate, phenprocoumon, sulfatide, tinzaparin sodium, retaplase;

trifenagrel, warfarin, dextrans and the like; abciximab, acadesine, anipamil, argatroban, aspirin, clopidogrel, diadenosine 5',5'''-P1,P4-tetraphosphate (Ap4A) analogs, difibrotide, dilazep dihydrochloride, dipyridamole, dopamine, 3-methoxytyramine, glucagon, glycoprotein IIb/IIIa antagonists, such as, for example, Ro-43-8857, L-700,462, iloprost, isocarbacyclin methyl ester, itazigrel, ketanserin, BM-13.177, lamifiban, lifarizine, molsidomine, nifedipine, oxagrelate, prostaglandins, platelet activating factor antagonists such as, for example, lexipafant, prostacyclins, pyrazines, pyridinol carbamate, ReoPro (i.e., abciximab), sulfinpyrazone, synthetic compounds BN-50727, BN-52021, CV-4151, E-5510, FK-409, GU-7, KB-2796, KBT-3022, KC-404, KF-4939, OP-41483, TRK-100, TA-3090, TFC-612, ZK-36374, 2,4,5,7-tetrathiaoctane, 2,4,5,7-tetrathiaoctane 2,2-dioxide, 2,4,5-trithiahexane, theophyllin pentoxifyllin, thromboxane and thromboxane synthetase inhibitors such as, for example, picotamide, sulotroban, ticlopidine, tirofiban, trapidil, ticlopidine, trifenagrel, trilinolein, 3-substituted 5,6-bis(4-methoxyphenyl)-1,2,4-triazines; antibodies to glycoprotein IIb/IIIa; anti-serotonin drugs, such as, for example, clopridogrel; sulfinpyrazone and the like; aspirin; dipyridamole; clofibrate; pyridinol carbamate; glucagon, caffeine; theophyllin pentoxifyllin; ticlopidine, and the like.

Suitable proton pump inhibitors include, but are not limited to, disulprazole, esomeprazole, lansoprazole, leminoprazole, omeprazole, pantoprazole, rabeprazole, timoprazole, tenatoprazole, 2-(2-benzimidazolyl)-pyridine, tricyclic imidazole, thienopydidine benzimidazole, fluoroalkoxy substituted benzimidazole, dialkoxy benzimidazole, N-substituted 2-(pyridylalkenesulfinyl) benzimidazole, cycloheptenepyridine, 5-pyrrolyl-2-pyridylmethylsulfinyl benzimidazole, alkylsulfinyl benzimidazole, fluoro-pyridylmethylsulfinyl benzimidazole, imidazo(4,5-b)pydridine, RO 18-5362, IY 81149, 4-amino-3-carbonyl quinoline, 4-amino-3-acylnaphthyride, 4-aminoquinoline, 4-amino-3-acylquinoline, 3-butyryl-4-(2-methylphenylamino)-8-(2-hydroxyethoxy)quinoline, quinazoline, tetrahydroisoquinolin-2-yl pyrimidine, YH 1885, 3-substituted 1,2,4-thiadiazolo(4,5-a) benzimidazole, 3-substituted imidazo(1,2-d)-thiadiazole, 2-sulfinylnicotinamide, pyridylsulfinylbenz imidazole, pyridylsulfinyl thieno imidazole, theinoimidazole-toluidine, 4,5-dihydrooxazole, thienoimidazole-toluidine, Hoe-731, imidazo(1,2-a)pyridine, pyrrolo(2,3-b)pyridine,.and the like.

Suitable proton pump inhibitors are described more fully in the literature, such as in Goodman and Gilman, The Pharmacological Basis of Therapeutics (9th Edition), McGraw-Hill, 1995; the Merck Index on CD-ROM, 13th Edition; and in WO 00/50037 assigned to NitroMed Inc., the disclosures of which are incorporated herein by reference in their entirety.

Suitable renin inhibitors include, but are not limited to, aldosterone, aliskiren (SPP-100), ditekiren, enalkrein (A-64662), medullipin, terlkiren, tonin, zankiren, RO 42-5892 (remikiren), A 62198, A 64662, A 65317, A 69729, A 72517 (zankiren), A 74273, CP 80794, CGP 29287, CGP-38560A, EMD 47942, ES 305, ES 1005, ES 8891, FK 906, FK 744, H 113, H-142, KRI 1314, pepstatin A, RO 44-9375 (ciprokiren), RO 42-5892, RO 66-1132, RO 66-1168, SP 500, SP 800, SR-43845, SQ 34017, U 71038, YM-21095, YM-26365, urea derivatives of peptides, amino acids connected by nonpeptide bonds, di- and tri-peptide derivatives (e.g., Act-A, Act-B, Act-C, ACT-D, and the like), amino acids and derivatives thereof, diol sulfonamides and sulfinyls, modified peptides, peptidyl beta-aminoacyl aminodiol carbamates, monoclonal antibodies to renin. Suitable renin inhibitors are described more fully in U.S. Patent Nos. 5,116,835, 5,114,937, 5,106,835, 5,104,869, 5,095,119, 5,098,924), 5,095,006, 5,089,471, 5,075,451, 5,066,643, 5,063,208, 4,845,079, 5,055,466, 4,980,283, 4,885,292), 4,780,401, 5,071,837, 5,064,965, 5,063,207, 5,036,054, 5,036,053, 5,034,512, and 4,894,437, the disclosures of each of which are incorporated herein by reference in their entirety; and in the literature, such as in Goodman and Gilman, The Pharmacological Basis of Therapeutics (9th Edition), McGraw-Hill, 1995; and the Merck Index on CD-ROM, Thirteenth Edition; and on STN Express, file phar and file registry.

Suitable COX-2 inhibitors include, but are not limited to, nimesulide, celecoxib (CELEBREX®), etoricoxib (ARCOXIA®), flosulide, lumiracoxib (PREXIG®, COX-189), parecoxib (DYNSTAT®), rofecoxib (VIOXX®), tiracoxib (JTE-522), valdecoxib (BEXTRA®), ABT 963, BMS 347070, CS 502, DuP 697, GW-406381, NS-386, SC-57666, SC-58125, SC-58635, and the like, and mixtures of two or more thereof. Suitable COX-2 inhibitors are in U.S. Patent Nos. 5,344,991, 5,380,738, 5,393,790, 5,409,944, 5,434,178, 5,436,265, 5,466,823, 5,474,995, 5,510,368, 5,536,752,

5,550,142, 5,552,422, 5,604,253, 5,604,260, 5,639,780, 5,932,598 and 6,633,272, and in WO 94/03387, WO 94/15723, WO 94/20480, WO 94/26731, WO 94/27980, WO 95/00501, WO 95/15316, WO 96/03387, WO 96/03388, WO 96/06840, WO 96/21667, WO 96/31509, WO 96/36623, WO 97/14691, WO 97/16435, WO 01/45703 and WO 01/87343, the disclosures of each of which are incorporated herein by reference in their entirety; and in the literature, such as in Goodman and Gilman, The Pharmacological Basis of Therapeutics (9th Edition), McGraw-Hill, 1995; and the Merck Index on CD-ROM, Thirteenth Edition; and on STN Express, file phar and file registry.

In some embodiments the COX-2 inhibitors are celecoxib, etoracoxib, lumiracoxib, paracoxib, rofecoxib or valdecoxib. In more particular embodiments the celecoxib is administered in an amount of about 100 milligrams to about 800 milligrams as a single dose or as multiple doses per day; the etoricoxib is administered in an amount of about 50 milligrams to about 200 milligrams as a single does or as multiple doses per day; the lumiracoxib is administered in an amount of about 40 milligrams to about 1200 milligrams as a single does or as multiple doses per day; the paracoxib is administered in an amount of about 20 milligrams to about 100 milligrams as a single does or as multiple doses per day; the rofecoxib is administered in an amount of about 12.5 milligrams to about 50 milligrams as a single does or as multiple doses per day; the valdecoxib is administered in an amount of about 10 milligrams to about 40 milligrams as a single does or as multiple doses per day.

The invention provides compositions comprising (i) a nitrosated glutamic acid compound of the invention or pharmaceutically acceptable salt thereof, and (ii) at least one compound selected from the group consisting of aldosterone antagonists, angiotensin II antagonists, angiotensin-converting enzyme (ACE) inhibitors, β-adrenergic antagonists, diuretics, and hydralazine compounds in one or more pharmaceutically acceptable carriers. In other embodiments of the invention the aldosterone antagonist is eplerenone or spironolactone; the angiotensin II antagonist is candesartan cilexetil, eprosartan mesylate, irbesartan, losartan potassium, medoxomil, telmisartan, trandolapril, trandolaprilat or valsartan; the angiotensin-converting enzyme inhibitor is benazepril hydrochloride, captopril, enalapril maleate, fosinopril sodium, lisinopril, moexipril hydrochloride, quinapril hydrochloride; the β-adrenergic antagonist

is bisoprolol fumarate, carvedilol, metoprolol tartrate, propranolol hydrochloride or timolol maleate; the diuretic is amiloride hydrochloride, chlorthalidone, hydrochlorothiazide or triamterene; and the hydralazine compound is hydralazine hydrochloride.

The invention provides methods for treating cardiovascular disorders by administering to the patient in need thereof a therapeutically effective amount of the compounds and/or compositions described herein. For example, the patient can be administered a therapeutically effective amount of at least one nitrosated glutamic acid compound. In another embodiment, the patient can be administered a therapeutically effective amount of at least one nitrosated glutamic acid compound, and at least one nitric oxide donor compound. In yet another embodiment, the patient can be administered a therapeutically effective amount of at least one nitrosated glutamic acid compound, and, at least one therapeutic agent, including but not limited to, such as, for example, aldosterone antagonists, alpha-adrenergic receptor antagonists, angiotensin II antagonists, angiotensin-converting enzyme (ACE) inhibitors, antidiabetic compounds, anti-hyperlipidemic compounds, antioxidants, antithrombotic and vasodilator compounds, β-adrenergic antagonists, calcium channel blockers, diuretics, digitalis, cardiovascular, endothelin antagonists, hydralazine compounds, H_2 receptor antagonists, neutral endopeptidase inhibitors, nonsteroidal antiinflammatory compounds (NSAIDs), phosphodiesterase inhibitors, potassium channel blockers, platelet reducing agents, proton pump inhibitors, renin inhibitors, selective cyclooxygenase-2 (COX-2) inhibitors, and combinations of two or more thereof. In another embodiment, the patient can be administered a therapeutically effective amount of at least one nitrosated glutamic acid compound, and, at least one therapeutic agent, and, at least one nitric oxide donor compound. In one embodiment the cardiovascular disorder is hypertension, congestive heart failure and/or diastolic dysfunction. The nitrosated glutamic acid compound, nitric oxide donors, and/or therapeutic agents can be administered separately or as components of the same composition in one or more pharmaceutically acceptable carriers.

The invention provides methods for treating renovascular diseases by administering to the patient in need thereof a therapeutically effective amount of the

compounds and/or compositions described herein. For example, the patient can be administered a therapeutically effective amount of at least one nitrosated glutamic acid compound. In another embodiment, the patient can be administered a therapeutically effective amount of at least one nitrosated glutamic acid compound, and at least one nitric oxide donor compound. In yet another embodiment, the patient can be administered a therapeutically effective amount of at least one nitrosated glutamic acid compound, and, at least one therapeutic agent, including but not limited to, such as, for example, aldosterone antagonists, alpha-adrenergic receptor antagonists, angiotensin II antagonists, angiotensin-converting enzyme (ACE) inhibitors, antidiabetic compounds, anti-hyperlipidemic compounds, antioxidants, antithrombotic and vasodilator compounds, β-adrenergic antagonists, calcium channel blockers, digitalis, diuretics, endothelin antagonists, hydralazine compounds, H_2 receptor antagonists, neutral endopeptidase inhibitors, nonsteroidal antiinflammatory compounds (NSAIDs), phosphodiesterase inhibitors, potassium channel blockers, platelet reducing agents, proton pump inhibitors, renin inhibitors, selective cyclooxygenase-2 (COX-2) inhibitors, and combinations of two or more thereof. In another embodiment, the patient can be administered a therapeutically effective amount of at least one nitrosated glutamic acid compound, and, at least one therapeutic agent, and, at least one nitric oxide donor compound. In one embodiment the renovascular disease is renal failure or renal insufficiency. The nitrosated glutamic acid compound, nitric oxide donors, and/or therapeutic agents can be administered separately or as components of the same composition in one or more pharmaceutically acceptable carriers.

The invention provides methods for treating diabetes; treating diseases resulting from oxidative stress; treating endothelial dysfunctions; treating diseases caused by endothelial dysfunctions; treating cirrhosis; treating pre-eclampsia; treating osteoporosis; and treating nephropathy by administering to the patient in need thereof a therapeutically effective amount of the compounds and/or compositions described herein. For example, the patient can be administered a therapeutically effective amount of at least one nitrosated glutamic acid compound. In another embodiment, the patient can be administered a therapeutically effective

amount of at least one nitrosated glutamic acid compound, and at least one nitric oxide donor compound. In yet another embodiment, the patient can be administered a therapeutically effective amount of at least one nitrosated glutamic acid compound, and, at least one therapeutic agent, including but not limited to, such as, for example, aldosterone antagonists, alpha-adrenergic receptor antagonists, angiotensin II antagonists, angiotensin-converting enzyme (ACE) inhibitors, antidiabetic compounds, anti-hyperlipidemic compounds, antioxidants, antithrombotic and vasodilator compounds, β-adrenergic antagonists, calcium channel blockers, digitalis, diuretics, endothelin antagonists, hydralazine compounds, H_2 receptor antagonists, neutral endopeptidase inhibitors, nonsteroidal antiinflammatory compounds (NSAIDs), phosphodiesterase inhibitors, potassium channel blockers, platelet reducing agents, proton pump inhibitors, renin inhibitors, selective cyclooxygenase-2 (COX-2) inhibitors, and combinations of two or more thereof. In another embodiment, the patient can be administered a therapeutically effective amount of at least one nitrosated glutamic acid compound, and, at least one therapeutic agent, and, at least one nitric oxide donor compound. The nitrosated glutamic acid compounds, nitric oxide donors, and/or therapeutic agents can be administered separately or as components of the same composition in one or more pharmaceutically acceptable carriers.

The invention provides methods for treating diseases resulting from elevated levels of gamma-glutamyl transpeptidase and for the targeted delivery of compounds and nitric oxide to organs, cells or tissues containing the enzyme gamma-glutamyl transpeptidase by administering to the patient in need thereof a therapeutically effective amount of the compounds and/or compositions described herein. For example, the patient can be administered a therapeutically effective amount of at least one nitrosated glutamic acid compound, In another embodiment, the patient can be administered a therapeutically effective amount of at least one nitrosated glutamic acid compound, and at least one nitric oxide donor compound. In yet another embodiment, the patient can be administered a therapeutically effective amount of at least one nitrosated glutamic acid compound, and, at least one therapeutic agent, including but not limited to, such as, for example, aldosterone

antagonists, alpha-adrenergic receptor antagonists, angiotensin II antagonists, angiotensin-converting enzyme (ACE) inhibitors, antidiabetic compounds, anti-hyperlipidemic compounds, antioxidants, antithrombotic and vasodilator compounds, β-adrenergic antagonists, calcium channel blockers, digitalis, diuretics, endothelin antagonists, hydralazine compounds, H_2 receptor antagonists, neutral endopeptidase inhibitors, nonsteroidal antiinflammatory compounds (NSAIDs), phosphodiesterase inhibitors, potassium channel blockers, platelet reducing agents, proton pump inhibitors, renin inhibitors, selective cyclooxygenase-2 (COX-2) inhibitors, and combinations of two or more thereof. In another embodiment, the patient can be administered a therapeutically effective amount of at least one nitrosated glutamic acid compound, and, at least one therapeutic agent, and, at least one nitric oxide donor compound. The nitrosated glutamic acid compounds, nitric oxide donors, and/or therapeutic agents can be administered separately or as components of the same composition in one or more pharmaceutically acceptable carriers.

When administered separately, the glutamic acid compound, nitric oxide donor and/or therapeutic agent can be administered about the same time as part of the overall treatment regimen, i.e., as a combination therapy. "About the same time" includes administering the nitrosated glutamic acid compound simultaneously, sequentially, at the same time, at different times on the same day, or on different days, as long as they are administered as part of an overall treatment regimen, i.e., combination therapy or a therapeutic cocktail.

When administered in vivo, the compounds and compositions of the invention can be administered in combination with pharmaceutically acceptable carriers and in dosages described herein. When the compounds and compositions of the invention are administered as a combination of at least one nitrosated glutamic acid compound and/or at least one nitric oxide donor and/or therapeutic agent, they can also be used in combination with one or more additional compounds which are known to be effective against the specific disease state targeted for treatment. The nitric oxide donors, therapeutic agents and/or other additional compounds can be administered simultaneously with, subsequently to, or prior to administration of the nitrosated

glutamic acid compound.

The compounds and compositions of the invention can be administered by any available and effective delivery system including, but not limited to, orally, bucally, parenterally, by inhalation, by topical application, by injection, transdermally, or rectally (e.g., by the use of suppositories) in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles, as desired. Parenteral includes subcutaneous injections, intravenous, intramuscular, intrasternal injection, or infusion techniques. In one embodiment of the invention the nitrosated glutamic acid compound is administered orally, parentally or by inhalation.

Transdermal compound administration, which is known to one skilled in the art, involves the delivery of pharmaceutical compounds via percutaneous passage of the compound into the systemic circulation of the patient. Topical administration can also involve the use of transdermal administration such as transdermal patches or iontophoresis devices. Other components can be incorporated into the transdermal patches as well. For example, compositions and/or transdermal patches can be formulated with one or more preservatives or bacteriostatic agents including, but not limited to, methyl hydroxybenzoate, propyl hydroxybenzoate, chlorocresol, benzalkonium chloride, and the like. Dosage forms for topical administration of the compounds and compositions can include creams, sprays, lotions, gels, ointments, eye drops, nose drops, ear drops, and the like. In such dosage forms, the compositions of the invention can be mixed to form white, smooth, homogeneous, opaque cream or lotion with, for example, benzyl alcohol 1% or 2% (wt/wt) as a preservative, emulsifying wax, glycerin, isopropyl palmitate, lactic acid, purified water and sorbitol solution. In addition, the compositions can contain polyethylene glycol 400. They can be mixed to form ointments with, for example, benzyl alcohol 2% (wt/wt) as preservative, white petrolatum, emulsifying wax, and tenox II (butylated hydroxyanisole, propyl gallate, citric acid, propylene glycol). Woven pads or rolls of bandaging material, e.g., gauze, can be impregnated with the compositions in solution, lotion, cream, ointment or other such form can also be used for topical application. The compositions can also be applied topically using a transdermal system, such as one of an acrylic-based polymer adhesive with a resinous crosslinking agent impregnated with

the composition and laminated to an impermeable backing.

The compositions can also be applied topically using a transdermal system, such as one of an acrylic-based polymer adhesive with a resinous crosslinking agent impregnated with the composition and laminated to an impermeable backing. In a particular embodiment, the compositions of the invention are administered as a transdermal patch, more particularly as a sustained-release transdermal patch. The transdermal patches of the invention can include any conventional form such as, for example, adhesive matrix, polymeric matrix, reservoir patch, matrix or monolithic-type laminated structure, and are generally comprised of one or more backing layers, adhesives, penetration enhancers, an optional rate controlling membrane and a release liner which is removed to expose the adhesives prior to application. Polymeric matrix patches also comprise a polymeric-matrix forming material. Suitable transdermal patches are described in more detail in, for example, U. S. Patent Nos. 5,262,165, 5,948,433, 6,010,715 and 6,071,531, the disclosure of each of which are incorporated herein in their entirety.

Solid dosage forms for oral administration can include capsules, sustained-release capsules, tablets, sustained release tablets, chewable tablets, sublingual tablets, effervescent tablets, pills, powders, granules and gels. In such solid dosage forms, the active compounds can be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms can also comprise, as in normal practice, additional substances other than inert diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets, effervescent tablets, and pills, the dosage forms can also comprise buffering agents. Soft gelatin capsules can be prepared to contain a mixture of the active compounds or compositions of the invention and vegetable oil. Hard gelatin capsules can contain granules of the active compound in combination with a solid, pulverulent carrier such as lactose, saccharose, sorbitol, mannitol, potato starch, corn starch, amylopectin, cellulose derivatives of gelatin. Tablets and pills can be prepared with enteric coatings.

Liquid dosage forms for oral administration can include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions can also comprise

adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

Suppositories for vaginal or rectal administration of the compounds and compositions of the invention, such as for treating pediatric fever and the like, can be prepared by mixing the compounds or compositions with a suitable nonirritating excipient such as cocoa butter and polyethylene glycols which are solid at room temperature but liquid at rectal temperature, such that they will melt in the rectum and release the drug.

Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions can be formulated according to the known art using suitable dispersing agents, wetting agents and/or suspending agents. The sterile injectable preparation can also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that can be used are water, Ringer's solution, and isotonic sodium chloride solution. Sterile fixed oils are also conventionally used as a solvent or suspending medium.

The compositions of this invention can further include conventional excipients, i.e., pharmaceutically acceptable organic or inorganic carrier substances suitable for parenteral application which do not deleteriously react with the active compounds. Suitable pharmaceutically acceptable carriers include, for example, water, salt solutions, alcohol, vegetable oils, polyethylene glycols, gelatin, lactose, amylose, magnesium stearate, talc, surfactants, silicic acid, viscous paraffin, perfume oil, fatty acid monoglycerides and diglycerides, petroethral fatty acid esters, hydroxymethyl-cellulose, polyvinylpyrrolidone, and the like. The pharmaceutical preparations can be sterilized and if desired, mixed with auxiliary agents, e.g., lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, colorings, flavoring and/or aromatic substances and the like which do not deleteriously react with the active compounds. For parenteral application, particularly suitable vehicles consist of solutions, preferably oily or aqueous solutions, as well as suspensions, emulsions, or implants. Aqueous suspensions may contain substances which increase the viscosity of the suspension and include, for example, sodium

carboxymethyl cellulose, sorbitol and/or dextran. Optionally, the suspension may also contain stabilizers.

The composition, if desired, can also contain minor amounts of wetting agents, emulsifying agents and/or pH buffering agents. The composition can be a liquid solution, suspension, emulsion, tablet, pill, capsule, sustained release formulation, or powder. The composition can be formulated as a suppository, with traditional binders and carriers such as triglycerides. Oral formulations can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, and the like.

Various delivery systems are known and can be used to administer the compounds or compositions of the invention, including, for example, encapsulation in liposomes, microbubbles, emulsions, microparticles, microcapsules and the like. The required dosage can be administered as a single unit or in a sustained release form.

The bioavailability of the compositions can be enhanced by micronization of the formulations using conventional techniques such as grinding, milling, spray drying and the like in the presence of suitable excipients or agents such as phospholipids or surfactants.

Sustained release dosage forms of the invention may comprise microparticles and/or nanoparticles having a therapeutic agent dispersed therein or may comprise the therapeutic agent in pure, preferably crystalline, solid form. For sustained release administration, microparticle dosage forms comprising pure, preferably crystalline, therapeutic agents are preferred. The therapeutic dosage forms of this aspect of the invention may be of any configuration suitable for sustained release.

Nanoparticle sustained release therapeutic dosage forms are preferably biodegradable and, optionally, bind to the vascular smooth muscle cells and enter those cells, primarily by endocytosis. The biodegradation of the nanoparticles occurs over time (e.g., 30 to 120 days; or 10 to 21 days) in prelysosomic vesicles and lysosomes. Preferred larger microparticle therapeutic dosage forms of the invention release the therapeutic agents for subsequent target cell uptake with only a few of the smaller microparticles entering the cell by phagocytosis. A practitioner in the art will appreciate that the precise mechanism by which a target cell assimilates and

metabolizes a dosage form of the invention depends on the morphology, physiology and metabolic processes of those cells. The size of the particle sustained release therapeutic dosage forms is also important with respect to the mode of cellular assimilation. For example, the smaller nanoparticles can flow with the interstitial fluid between cells and penetrate the infused tissue. The larger microparticles tend to be more easily trapped interstitially in the infused primary tissue, and thus are useful to deliver anti-proliferative therapeutic agents.

Particular sustained release dosage forms of the invention comprise biodegradable microparticles or nanoparticles. More particularly, biodegradable microparticles or nanoparticles are formed of a polymer containing matrix that biodegrades by random, nonenzymatic, hydrolytic scissioning to release therapeutic agent, thereby forming pores within the particulate structure.

In a particular embodiment, the compositions of the invention are orally administered as a sustained release tablet or a sustained release capsule. For example, the sustained release formulations can comprise a therapeutically effective amount of at least one nitrosated glutamic acid compound or a pharmaceutically acceptable salt thereof, and, optionally at least one nitric oxide donor, or the sustained release formulations can comprise a therapeutically effective amount of at least one nitrosated glutamic acid compound or a pharmaceutically acceptable salt thereof, and at least one nitric oxide donor, and, optionally at least one therapeutic agent

The compounds and compositions of the invention can be formulated as pharmaceutically acceptable salt forms. Pharmaceutically acceptable salts include, for example, alkali metal salts and addition salts of free acids or free bases. The nature of the salt is not critical, provided that it is pharmaceutically-acceptable. Suitable pharmaceutically-acceptable acid addition salts may be prepared from an inorganic acid or from an organic acid. Examples of such inorganic acids include, but are not limited to, hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric and phosphoric acid and the like. Appropriate organic acids include, but are not limited to, aliphatic, cycloaliphatic, aromatic, heterocyclic, carboxylic and sulfonic classes of organic acids, such as, for example, formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic,

benzoic, anthranilic, mesylic, salicylic, p-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, toluenesulfonic, 2-hydroxyethanesulfonic, sulfanilic, stearic, algenic, β-hydroxybutyric, cyclohexylaminosulfonic, galactaric and galacturonic acid and the like. Suitable pharmaceutically-acceptable base addition salts include, but are not limited to, metallic salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc or organic salts made from primary, secondary and tertiary amines, cyclic amines, N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine and the like. All of these salts may be prepared by conventional means from the corresponding compound by reacting, for example, the appropriate acid or base with the compound. In one embodiment, the pharmaceutically acceptable salts of the compounds of the invention do not include the nitrate salt.

While individual needs may vary, determination of optimal ranges for effective amounts of the compounds and/or compositions is within the skill of the art. Generally, the dosage required to provide an effective amount of the compounds and compositions, which can be adjusted by one of ordinary skill in the art, will vary depending on the age, health, physical condition, sex, diet, weight, extent of the dysfunction of the recipient, frequency of treatment and the nature and scope of the dysfunction or disease, medical condition of the patient, the route of administration, pharmacological considerations such as the activity, efficacy, pharmacokinetic and toxicology profiles of the particular compound used, whether a drug delivery system is used, and whether the compound is administered as part of a drug combination.

The amount of a given nitrosated glutamic acid compound of the invention that will be effective in the treatment of a particular disorder or condition will depend on the nature of the disorder or condition, and can be determined by standard clinical techniques, including reference to Goodman and Gilman, supra; The Physician's Desk Reference, Medical Economics Company, Inc., Oradell, N.J., 1995; and Drug Facts and Comparisons, Inc., St. Louis, MO, 1993. The precise dose to be used in the formulation will also depend on the route of administration, and the seriousness of the disease or disorder, and should be decided by the physician and the patient's circumstances.

The invention also provides pharmaceutical kits comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compounds and/or compositions of the invention, including, at least, one or more of the novel nitrosated glutamic acid compounds, and one or more of the NO donors described herein. Associated with such kits can be additional therapeutic agents or compositions (e.g., aldosterone antagonists, alpha-adrenergic receptor antagonists, angiotensin II antagonists, angiotensin-converting enzyme (ACE) inhibitors, antidiabetic compounds, anti-hyperlipidemic compounds, antioxidants, antithrombotic and vasodilator compounds, β-adrenergic antagonists, calcium channel blockers, digitalis, diuretics, endothelin antagonists, hydralazine compounds, H_2 receptor antagonists, neutral endopeptidase inhibitors, nonsteroidal antiinflammatory compounds (NSAIDs), phosphodiesterase inhibitors, potassium channel blockers, platelet reducing agents, proton pump inhibitors, renin inhibitors, selective cyclooxygenase-2 (COX-2) inhibitors, and the like, and combinations of two or more thereof), devices for administering the compositions, and notices in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products which reflects approval by the agency of manufacture, use or sale for humans.

The compounds and compositions of the invention can be administered by any available and effective delivery system including, but not limited to, orally, bucally, parenterally, by inhalation spray, by topical application, by injection, transdermally, or rectally (e.g., by the use of suppositories) in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles, as desired. Parenteral includes subcutaneous injections, intravenous, intramuscular, intrasternal injection, or infusion techniques. In a preferred embodiment the nitrosated glutamic acid compound are administered parenterally.

Transdermal compound administration, which is known to one skilled in the art, involves the delivery of pharmaceutical compounds via percutaneous passage of the compound into the systemic circulation of the patient. Topical administration can also involve the use of transdermal administration such as transdermal patches or iontophoresis devices. Other components can be incorporated into the transdermal patches as well. For example, compositions and/or transdermal patches can be

formulated with one or more preservatives or bacteriostatic agents including, but not limited to, methyl hydroxybenzoate, propyl hydroxybenzoate, chlorocresol, benzalkonium chloride, and the like. Dosage forms for topical administration of the compounds and compositions can include creams, sprays, lotions, gels, ointments, eye drops, nose drops, ear drops, and the like. In such dosage forms, the compositions of the invention can be mixed to form white, smooth, homogeneous, opaque cream or lotion with, for example, benzyl alcohol 1% or 2% (wt/wt) as a preservative, emulsifying wax, glycerin, isopropyl palmitate, lactic acid, purified water and sorbitol solution. In addition, the compositions can contain polyethylene glycol 400. They can be mixed to form ointments with, for example, benzyl alcohol 2% (wt/wt) as preservative, white petrolatum, emulsifying wax, and tenox II (butylated hydroxyanisole, propyl gallate, citric acid, propylene glycol). Woven pads or rolls of bandaging material, e.g., gauze, can be impregnated with the compositions in solution, lotion, cream, ointment or other such form can also be used for topical application. The compositions can also be applied topically using a transdermal system, such as one of an acrylic-based polymer adhesive with a resinous crosslinking agent impregnated with the composition and laminated to an impermeable backing.

The compositions can also be applied topically using a transdermal system, such as one of an acrylic-based polymer adhesive with a resinous crosslinking agent impregnated with the composition and laminated to an impermeable backing. In a particular embodiment, the compositions of the invention are administered as a transdermal patch, more particularly as a sustained-release transdermal patch. The transdermal patches of the invention can include any conventional form such as, for example, adhesive matrix, polymeric matrix, reservoir patch, matrix or monolithic-type laminated structure, and are generally comprised of one or more backing layers, adhesives, penetration enhancers, an optional rate controlling membrane and a release liner which is removed to expose the adhesives prior to application. Polymeric matrix patches also comprise a polymeric-matrix forming material. Suitable transdermal patches are described in more detail in, for example, U. S. Patent Nos. 5,262,165, 5,948,433, 6,010,715 and 6,071,531, the disclosure of each of which are incorporated herein in their entirety.

Solid dosage forms for oral administration can include capsules, sustained-release capsules, tablets, sustained release tablets, chewable tablets, sublingual tablets, effervescent tablets, pills, powders, granules and gels. In such solid dosage forms, the active compounds can be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms can also comprise, as in normal practice, additional substances other than inert diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets, effervescent tablets, and pills, the dosage forms can also comprise buffering agents. Soft gelatin capsules can be prepared to contain a mixture of the active compounds or compositions of the invention and vegetable oil. Hard gelatin capsules can contain granules of the active compound in combination with a solid, pulverulent carrier such as lactose, saccharose, sorbitol, mannitol, potato starch, corn starch, amylopectin, cellulose derivatives of gelatin. Tablets and pills can be prepared with enteric coatings.

Liquid dosage forms for oral administration can include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions can also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

Suppositories for vaginal or rectal administration of the compounds and compositions of the invention, such as for treating pediatric fever and the like, can be prepared by mixing the compounds or compositions with a suitable nonirritating excipient such as cocoa butter and polyethylene glycols which are solid at room temperature but liquid at rectal temperature, such that they will melt in the rectum and release the drug.

Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions can be formulated according to the known art using suitable dispersing agents, wetting agents and/or suspending agents. The sterile injectable preparation can also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that can be used are water, Ringer's solution, and isotonic sodium chloride solution. Sterile fixed oils are also conventionally used as a solvent or

suspending medium.

The compositions of this invention can further include conventional excipients, i.e., pharmaceutically acceptable organic or inorganic carrier substances suitable for parenteral application which do not deleteriously react with the active compounds. Suitable pharmaceutically acceptable carriers include, for example, water, salt solutions, alcohol, vegetable oils, polyethylene glycols, gelatin, lactose, amylose, magnesium stearate, talc, surfactants, silicic acid, viscous paraffin, perfume oil, fatty acid monoglycerides and diglycerides, petroethral fatty acid esters, hydroxymethyl-cellulose, polyvinylpyrrolidone, and the like. The pharmaceutical preparations can be sterilized and if desired, mixed with auxiliary agents, e.g., lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, colorings, flavoring and/or aromatic substances and the like which do not deleteriously react with the active compounds. For parenteral application, particularly suitable vehicles consist of solutions, preferably oily or aqueous solutions, as well as suspensions, emulsions, or implants. Aqueous suspensions may contain substances which increase the viscosity of the suspension and include, for example, sodium carboxymethyl cellulose, sorbitol and/or dextran. Optionally, the suspension may also contain stabilizers.

The composition, if desired, can also contain minor amounts of wetting agents, emulsifying agents and/or pH buffering agents. The composition can be a liquid solution, suspension, emulsion, tablet, pill, capsule, sustained release formulation, or powder. The composition can be formulated as a suppository, with traditional binders and carriers such as triglycerides. Oral formulations can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, and the like.

Various delivery systems are known and can be used to administer the compounds or compositions of the invention, including, for example, encapsulation in liposomes, microbubbles, emulsions, microparticles, microcapsules and the like. The required dosage can be administered as a single unit or in a sustained release form.

The bioavailabilty of the compositions can be enhanced by micronization of the formulations using conventional techniques such as grinding, milling, spray drying and

the like in the presence of suitable excipients or agents such as phospholipids or surfactants.

Sustained release dosage forms of the invention may comprise microparticles and/or nanoparticles having a therapeutic agent dispersed therein or may comprise the therapeutic agent in pure, preferably crystalline, solid form. For sustained release administration, microparticle dosage forms comprising pure, preferably crystalline, therapeutic agents are preferred. The therapeutic dosage forms of this aspect of the invention may be of any configuration suitable for sustained release.

Nanoparticle sustained release therapeutic dosage forms are preferably biodegradable and, optionally, bind to the vascular smooth muscle cells and enter those cells, primarily by endocytosis. The biodegradation of the nanoparticles occurs over time (e.g., 30 to 120 days; or 10 to 21 days) in prelysosomic vesicles and lysosomes. Preferred larger microparticle therapeutic dosage forms of the invention release the therapeutic agents for subsequent target cell uptake with only a few of the smaller microparticles entering the cell by phagocytosis. A practitioner in the art will appreciate that the precise mechanism by which a target cell assimilates and metabolizes a dosage form of the invention depends on the morphology, physiology and metabolic processes of those cells. The size of the particle sustained release therapeutic dosage forms is also important with respect to the mode of cellular assimilation. For example, the smaller nanoparticles can flow with the interstitial fluid between cells and penetrate the infused tissue. The larger microparticles tend to be more easily trapped interstitially in the infused primary tissue, and thus are useful to deliver anti-proliferative therapeutic agents.

Particular sustained release dosage forms of the invention comprise biodegradable microparticles or nanoparticles. More particularly, biodegradable microparticles or nanoparticles are formed of a polymer containing matrix that biodegrades by random, nonenzymatic, hydrolytic scissioning to release therapeutic agent, thereby forming pores within the particulate structure.

The compounds and compositions of the invention can be formulated as pharmaceutically acceptable salt forms. Pharmaceutically acceptable salts include, for example, alkali metal salts and addition salts of free acids or free bases. The nature of

the salt is not critical, provided that it is pharmaceutically-acceptable. Suitable pharmaceutically-acceptable acid addition salts may be prepared from an inorganic acid or from an organic acid. Examples of such inorganic acids include, but are not limited to, hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric and phosphoric acid and the like. Appropriate organic acids include, but are not limited to, aliphatic, cycloaliphatic, aromatic, heterocyclic, carboxylic and sulfonic classes of organic acids, such as, for example, formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, salicylic, p-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, toluenesulfonic, 2-hydroxyethanesulfonic, sulfanilic, stearic, algenic, β-hydroxybutyric, cyclohexylaminosulfonic, galactaric and galacturonic acid and the like. Suitable pharmaceutically-acceptable base addition salts include, but are not limited to, metallic salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc or organic salts made from primary, secondary and tertiary amines, cyclic amines, N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine and the like. All of these salts may be prepared by conventional means from the corresponding compound by reacting, for example, the appropriate acid or base with the compound.

While individual needs may vary, determination of optimal ranges for effective amounts of the compounds and/or compositions is within the skill of the art. Generally, the dosage required to provide an effective amount of the compounds and compositions, which can be adjusted by one of ordinary skill in the art, will vary depending on the age, health, physical condition, sex, diet, weight, extent of the dysfunction of the recipient, frequency of treatment and the nature and scope of the dysfunction or disease, medical condition of the patient, the route of administration, pharmacological considerations such as the activity, efficacy, pharmacokinetic and toxicology profiles of the particular compound used, whether a drug delivery system is used, and whether the compound is administered as part of a drug combination.

The amount of a given nitrosated glutamic acid compound of the invention that will be effective in the treatment of a particular disorder or condition will depend on the

nature of the disorder or condition, and can be determined by standard clinical techniques, including reference to Goodman and Gilman, supra; The Physician's Desk Reference, Medical Economics Company, Inc., Oradell, N.J., 1995; and Drug Facts and Comparisons, Inc., St. Louis, MO, 1993. The precise dose to be used in the formulation will also depend on the route of administration, and the seriousness of the disease or disorder, and should be decided by the physician and the patient's circumstances.

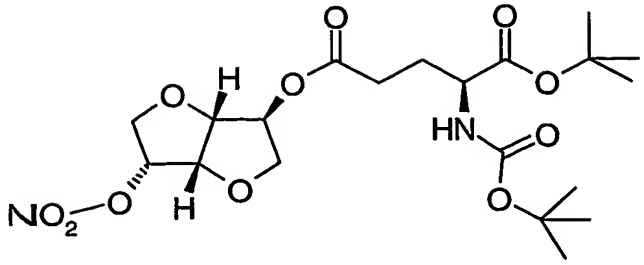
The invention also provides pharmaceutical kits comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compounds and/or compositions of the invention, including, at least, one or more of the novel nitrosated glutamic acid compound and/or at least one or more of the NO donors described herein. Associated with such kits can be additional therapeutic agents or compositions (e.g., aldosterone antagonists, alpha-adrenergic receptor antagonists, antidiabetic compounds, anti-hyperlipidemic drugs, angiotensin II antagonists, angiotensin-converting enzyme (ACE) inhibitors, antioxidants, antithrombotic and vasodilator drugs, beta-adrenergic blockers, calcium channel blockers, diuretics, endothelin antagonists, H_2 receptor antagonists, neutral endopeptidase inhibitors, nonsteroidal antiinflammatory compounds (NSAIDs), potassium channel blockers, platelet reducing agents, proton pump inhibitors, renin inhibitors, selective cyclooxygenase-2 (COX-2) inhibitors, and the like, and combinations of two or more thereof), devices for administering the compositions, and notices in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products which reflects approval by the agency of manufacture, use or sale for humans.

Examples

The following non-limiting examples further describe and enable one of ordinary skill in the art to make and use the present invention. In each of the examples, flash chromatography was performed on 40 micron silica gel (Baker).

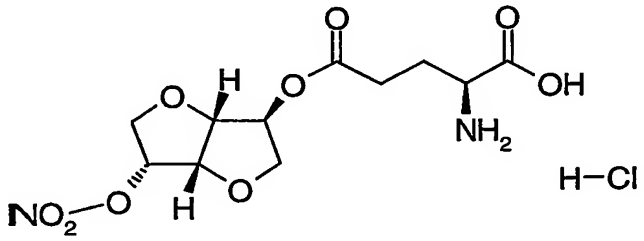
Example 1: (2S)-4-{[(1S,2S,5S,6R)-6-(Nitrooxy)-4,8-dioxabicyclo[3.3.0]oct-2-yl]oxycarbonyl}-2-aminobutanoic acid, hydrochloride salt

1a. (1S,2S,5S,6R)-6-(Nitrooxy)-4,8-dioxabicyclo[3.3.0]oct-2-yl tert-butyl (2S)-2-[(tert-butoxy)carbonylamino]pentane-1,5-dioate



BOC-L-Glutamic acid alpha tert-butyl ester (1.47 g, 4.84 mmol), DMAP (117.1 mg, 0.96 mmol), and isosorbide-5-mononitrate (1.02 g, 5.33 mmol) were dissolved in CH_2Cl_2 (15 mL) and EDAC (1.10 g, 5.80 mmol) was added. The solution was stirred at room temperature overnight. The sample was diluted with additional CH_2Cl_2 (10 mL) and washed with water and brine. The organics were separated, dried ($MgSO_4$) and the solvent removed under reduced pressure. The sample was purified via column chromatography on silica gel eluting with 3:1 hexanes/EtOAc to give the title compound as a clear oil (1.34 g, 58% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.37-5.29 (m, 1H), 5.22-5.21 (m, 1H), 5.07-5.05 (m, 1H), 4.99-4.96 (m, 1H), 4.49-4.47 (m, 1H), 4.06-4.02 (m, 2H), 4.00-3.99 (m, 1H), 3.92-3.86 (m, 1H), 2.49-2.31 (m, 2H), 2.19-2.08 (m, 1H), 2.01-1.82 (m, 1H), 1.46 (s, 9H), 1.43 (s, 9H). Mass spectrum (API-TIS) *m/z* 477 (M+ 1).

1b. (2S)-4-{[(1S,2S,5S,6R)-6-(Nitrooxy)-4,8-dioxabicyclo[3.3.0]oct-2-yl]oxycarbonyl}-2-aminobutanoic acid, hydrochloride salt

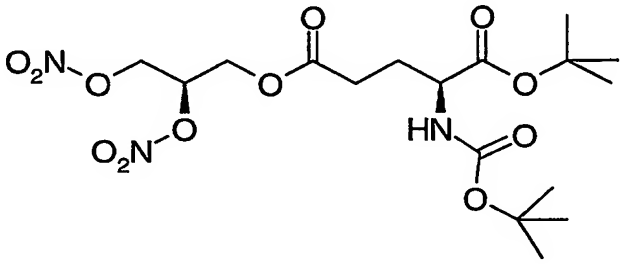


The product of Example 1a (1.34 g, 2.81 mmol) was taken up in EtOAc (10 mL) and HCl (10.6 g, 291 mmol) in EtOAc was added. The reaction mixture was allowed to stir at room temperature overnight. Hexane was added to the solution and the resulting solid collected via filtration to give the title compound as a white solid (0.71 g, 75% yield). Mp 160-162 °C ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.67-8.40 (m, 2H), 5.52 (dt, J = 2.1 and 5.4 Hz, 1H), 5.10 (d, J = 3.0 Hz, 1H), 4.97 (t, J = 5.4 Hz, 1H), 4.43 (d, J = 5.0 Hz, 1H), 3.98-3.94 (m, 2H), 3.82 (dd, J = 5.2 Hz, 11.5, 1H), 3.80 (dd, J = 3.3 Hz, 10.8,

1H), 3.34 (m, 3H), 2.61-2.47 (m, 2H), 2.09-1.99 (m, 2H). Mass spectrum (API-TIS) *m/z* 321 (M+ 1).

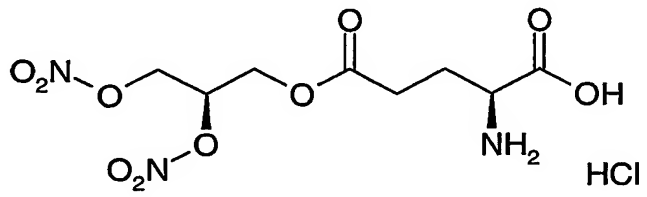
Example 2: 4-{{(2R)-2,3-Bis(nitrooxy)propyl]oxycarbonyl}(2S)-2-aminobutanoic acid, hydrochloride salt

2a. (2R)-2,3-Bis(nitrooxy)propyl tert-butyl (2S)-2-[(tert-butoxy)carbonylamino] pentane-1,5-dioate



BOC-L-Glutamic acid alpha tert-butyl ester (1.07 g, 3.53 mmol), (2S)-2,3-bis(nitrooxy)propan-1-ol (prepared as described in US 2004/0024057, Example 5d) (0.77 g, 4.23 mmol) and DMAP (85.4 mg, 0.71 mmol) were dissolved in CH_2Cl_2 (15 mL) and EDAC (0.81 g, 4.23 mmol) was added. The mixture was stirred at room temperature overnight. The solution was washed with water and brine. The organics were separated, dried ($MgSO_4$), and the solvent removed under reduced pressure. The sample was purified via column chromatography on silica gel eluting with 3:1 hexanes/EtOAc to yield the title compound as a yellow oil (1.44 g, 88% yield). ^1H NMR (300 MHz, $CDCl_3$) δ 5.11-5.08 (m, 1H), 4.68 (t, J = 4.6 Hz, 2H), 4.40-4.35 (m, 2H), 4.22-4.18 (m, 1H), 2.51-2.37 (m, 2H), 2.36-2.14 (m, 1H), 1.95-1.83 (m, 1H), 1.47 (s, 9H), 1.44 (s, 9H). Mass spectrum (API-TIS) *m/z* 468 (M+ 1).

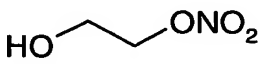
2b. 4-{{(2R)-2,3-Bis(nitrooxy)propyl]oxycarbonyl}(2S)-2-aminobutanoic acid, hydrochloride salt



The title compound will be prepared from the product of Example 2a using the procedure for Example 8c.

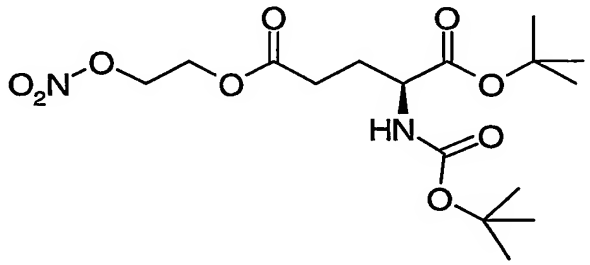
Example 3: (2S)-2-Amino-4-{[2-(nitrooxy)ethyl]oxycarbonyl}butanoic acid, 2,2,2-trifluoroacetic acid

3a. 2-(Nitrooxy)ethan-1-ol



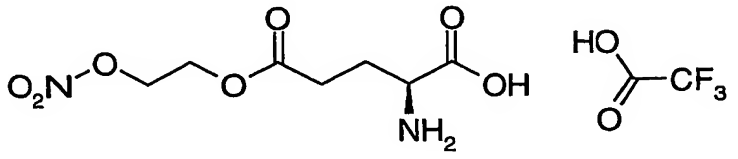
1-Bromoethanol (2.0 mL, 28.21 mmol) was dissolved in CH_3CN (50 mL) and $AgNO_3$ (9.58 g, 56.42 mmol) was added. The mixture was stirred at 60 °C for 12 h. Brine was added (20 mL) and the mixture stirred at room temperature for 1 h. The resulting solid was removed via filtration through Celite, the filtrate collected, and the solvent removed under reduced pressure. The resulting oily residue was diluted with CH_2Cl_2 (50 mL) and the sample washed with brine and dried. The solvent was removed under reduced pressure to give the title compound as a yellow oil (2.04 g, 68% yield). ^1H NMR (300 MHz, $CDCl_3$) δ 4.57 (t, J = 4.5 Hz, 2H), 3.90 (t, J = 4.5 Hz, 2H), 2.61-2.56 (m, 1H). Mass spectrum (API-TIS) *m/z* 108 (M+ 1).

3b. tert-Butyl 2-(nitrooxy)ethyl (2S)-2-[(tert-butoxy)carbonylamino]pentane-1,5-dioate



BOC-L-Glutamic acid alpha tert-butyl ester (4.81 g, 15.87 mmol), the product of Example 3a (2.04 g, 19.1 mmol), and DMAP (384.0 mg, 3.17 mmol)) were dissolved in CH_2Cl_2 (50 mL) and EDAC (3.64 g, 19.05 mmol) was added. The mixture was stirred at room temperature overnight. The solution was washed with water and brine. The organics were separated, dried ($MgSO_4$) and the solvent removed under reduced pressure. The sample was purified via column chromatography on silica gel eluting with 3:1 hexanes/EtOAc to yield the title compound as a yellow oil (5.76 g, 93% yield). ^1H NMR (300 MHz, $CDCl_3$) δ 5.11-5.08 (m, 1H), 4.68 (t, 2H, J = 4.6 Hz, 2H), 4.40-4.35 (m, 2H), 4.22-4.18 (m, 1H), 2.51-2.37 (m, 1H), 2.36-2.14 (m, 1H), 1.95-1.83 (m, 1H), 1.47 (s, 9H), 1.44 (s, 9H). Mass spectrum (API-TIS) *m/z* 393 (M+ 1).

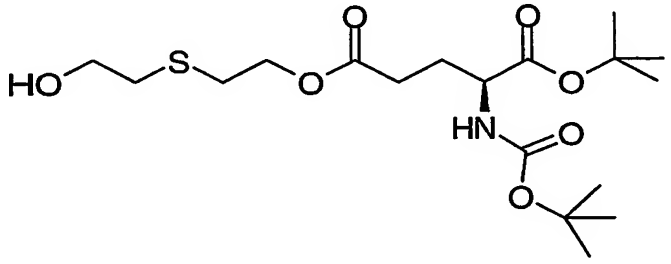
3c. (2S)-2-Amino-4-{[2-(nitrooxy)ethyl]oxycarbonyl}butanoic acid, 2,2,2-trifluoroacetic acid



The product of Example 3b (4.7 g, 12.0 mmol) was dissolved in CH_2Cl_2 (30 mL) and trifluoroacetic acid (5.8 mL, 72.2 mmol) was added dropwise. The mixture was stirred at room temperature for 3 hours and the solvent removed under reduced pressure. The resulting solid was dissolved in EtOAc (2 mL) and Et_2O (50 mL) was added. The resulting precipitate was collected via filtration to give the title compound (1.7 g, 40% yield) as a white solid: ^1H NMR (300 MHz, $CDCl_3$) δ 4.72-4.67 (m, 2H), 4.30-4.25 (m, 2H), 3.12-3.08 (m, 2H), 2.51-2.37 (m, 2H), 1.95-1.83 (m, 1H). Mass spectrum API-TIS- *m/z* 237 (MH^+).

Example 4: (2S)-2-Amino-4-[(2-(nitrooxy)ethyl]sulfonyl}ethyl)oxycarbonyl] butanoic acid, hydrochloride salt

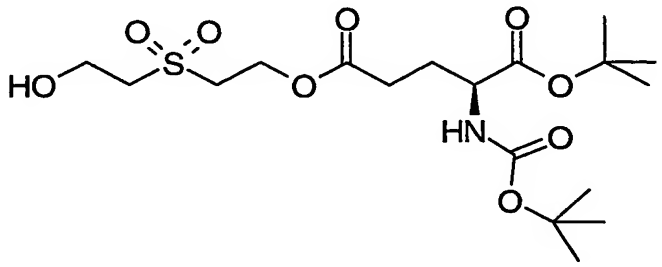
4a. tert-Butyl 2-(2-hydroxyethylthio)ethyl (2S)-2-[(tert-butoxy)carbonylamino] pentane-1,5-dioate



BOC-L-Glutamic acid alpha tert-butyl ester (1.65 g, 5.44 mmol), 2,2'-thiodiethanol (2.72 mL, 27.22 mmol) and DMAP (0.13 g, 1.08 mmol) were dissolved in CH_2Cl_2 (50 mL) and EDAC (1.25 g, 6.52 mmol) was added. The mixture was stirred at room temperature for 60 hours. The sample was washed with water and brine, dried over $MgSO_4$, and the solvent removed under reduced pressure. The sample was purified via column chromatography on silica gel eluting with 2:1 hexanes/EtOAc to yield the title compound as a yellow oil (1.56 g, 70% yield). ^1H NMR (300 MHz,

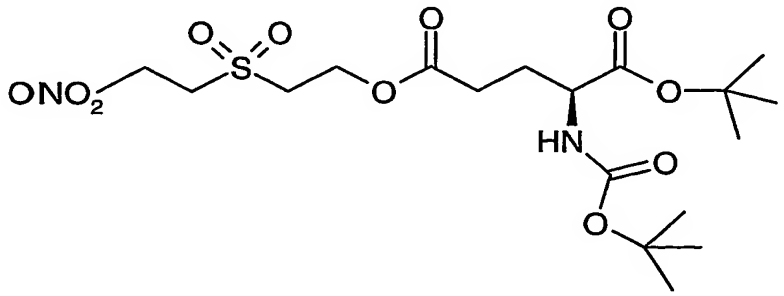
$CDCl_3$) δ 5.13-5.11 (m, 1H), 4.25-4.20 (m, 3H), 3.76-3.80 (m, 2H), 2.78-2.73 (m, 4H), 2.46-2.37 (m, 2H), 2.16-2.08 (m, 1H), 1.94-1.82 (m, 1H), 1.44 (s, 9H), 1.41 (s, 9H). Mass spectrum (API-TIS) *m/z* 408 (M+ 1).

4b. tert-Butyl 2-[(2-hydroxyethyl)sulfonyl]ethyl (2S)-2-[(tert-butoxy) carbonylamino]pentane-1,5-dioate



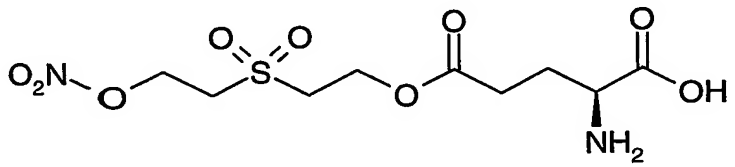
The product of Example 4a (1.56 g, 3.83 mmol) was dissolved in CH_2Cl_2 (50 mL) and Oxone® (3.06 g, 4.98 mmol) was added. The mixture was stirred at room temperature overnight. The resulting solid was removed via filtration and the filtrate collected, and washed with saturated $NaHCO_3$ (25 mL) and brine. The sample was dried ($MgSO_4$) and the solvent removed under reduced pressure. The sample was purified via column chromatography on silica gel eluting with 2:1 hexanes/EtOAc to give the title compound as an oil (0.47 g, 28% yield). ^1H NMR (300 MHz, $CDCl_3$) δ 5.29-5.26 (m, 1H), 4.49-4.42 (m, 2H), 4.06-3.97 (m, 3H), 3.47-3.35 (m, 2H), 3.20-3.17 (m, 2H), 2.38-2.31 (m, 2H), 2.09-2.03 (m, 1H), 1.84-1.79 (m, 1H), 1.37 (s, 9H), 1.34 (s, 9H). Mass spectrum (API-TIS) *m/z* 440 (M+ 1).

4c. tert-Butyl 2-{[2-(nitrooxy)ethyl]sulfonyl}ethyl (2S)-2-[(tert-butoxy) carbonylamino] pentane-1,5-dioate



Fuming nitric acid (402.9 µL, 10.1 mmol) was added to acetic anhydride (1.58 mL, 16.8 mmol) at 0 °C and the mixture stirred for 15 minutes. The product of Example 4b (1.48 g, 3.36 mmol) was added and the mixture stirred at 0 °C for 3 hours. The sample was neutralized with saturated $NaHCO_3$ solution and the organics separated and dried. The solvent was removed under reduced pressure and the sample purified via column chromatography on silica gel eluting with 2:1 hexanes/EtOAc to give the title compound as an oil (1.13g, 69% yield). ^1H NMR (300 MHz, $CDCl_3$) δ 5.19-5.16 (m, 1H), 4.85 (t, $J = 5.8$ Hz, 2H), 4.51-4.41 (m, 2H), 4.10-4.08 (m, 1H), 3.46 (t, $J = 5.8$ Hz, 2H), 3.38-3.34 (m, 2H), 2.42-2.32 (m, 1H), 2.12-1.97 (m, 1H), 1.85-1.81 (m, 1H), 1.38 (s, 9H), 1.35 (s, 9H). Mass spectrum (API-TIS) *m/z* 485 (M+ 1).

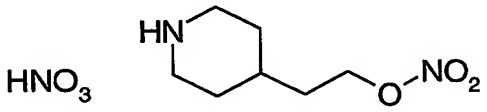
4d. (2S)-2-Amino-4-[(2-(nitrooxy)ethyl]sulfonyl}ethyl)oxycarbonyl]butanoic acid, hydrochloride salt



The title compound will be prepared from the product of Example 4c using the procedure for Example 8c.

Example 5: (2S)-2-Amino-5-{4-[2-(nitrooxy)ethyl]piperidyl}-5-oxopentanoic acid; hydrochloride salt

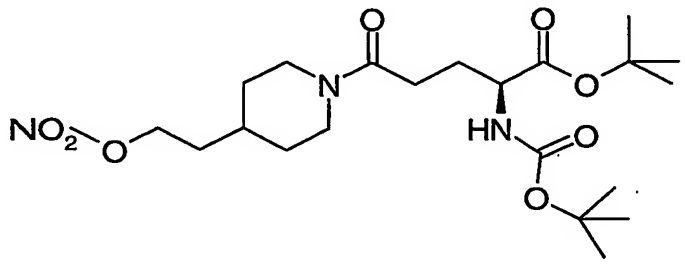
5a. Nitrooxy(2-(4-piperidyl)ethyl), nitric acid salt



4-Piperidylethan-1-ol (10 g, 77.3 mmol) in a mixture of EtOAc (90 mL) and CH_2Cl_2 (5 mL) was added drop-wise to a mixture of fuming HNO_3 (24.4 g, 16.3 mL, 387 mmol) and Ac_2O (63.2 g, 58.4 mL, 619 mmol) at –10 °C. The reaction mixture was stirred at –10 °C for 30 minutes and then diluted with EtOAc and hexane. The precipitate was collected by filtration and washed with hexane to give the title compound (7.5 g, 41% yield) as a white solid. Mp 86-88 °C. ^1H NMR (300 MHz, d_6-DMSO) δ 8.20-8.30 (bs, 1H), 8.05-8.20 (bs, 1H), 4.57 (t, $J = 6.2$ Hz, 2H), 3.15-3.30 (m,

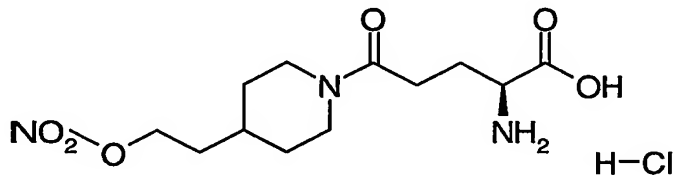
2H), 2.70-2.90 (m, 2H), 1.75-1.90 (m, 2H), 1.55-1.72 (m, 3H), 1.19-1.37 (m, 2H). ^{13}C NMR (75 MHz, d_6-DMSO) δ 71.6, 43.2, 31.9, 30.0, 28.1. Mass spectrum (API-TIS) *m/z* 175 (MH^+). Anal. calcd. for $C_7H_{15}N_3O_6$: C, 35.44; H, 6.37; N, 17.71. Found: C, 35.62; H, 6.39; N, 17.65.

5b. tert-Butyl (2S)-2-[(tert-butoxy)carbonylamino]-5-{4-[2-(nitrooxy)ethyl] piperidyl}-5-oxopentanoate



BOC-L-Glutamic acid alpha tert-butyl ester (2.95 g, 9.75 mmol), the product of Example 5a (2.04 g, 11.71 mmol), and DMAP (1.18 g, 9.75 mmol) were dissolved in CH_2Cl_2 (35 mL) and EDAC (2.23 g, 11.71 mmol) was added. The mixture was stirred at room temperature overnight. The sample was washed with water and brine, dried ($MgSO_4$) and the solvent removed under reduced pressure. Purification via column chromatography on silica gel eluting with 3:1 hexanes/EtOAc gave the title compound as a yellow oil (1.92 g, 43% yield). ^1H NMR (300 MHz, $CDCl_3$) δ 5.22 (m, 1H), 4.65-4.61 (m, 1H), 4.52-4.49 (m, 2H), 4.15-4.08 (m, 1H), 3.85-3.81 (m, 1H), 3.04-2.99 (m, 1H), 2.58-2.28 (m, 3H), 2.21-2.13 (m, 1H), 1.96-1.91 (m, 1H), 1.74-1.68 (m, 5H), 1.46 (s, 9H), 1.44 (s, 9H), 1.19-1.12 (m, 2H). Mass spectrum (API-TIS) *m/z* 460 (M+ 1).

5c. (2S)-2-Amino-5-{4-[2-(nitrooxy)ethyl]piperidyl}-5-oxopentanoic acid; hydrochloride salt

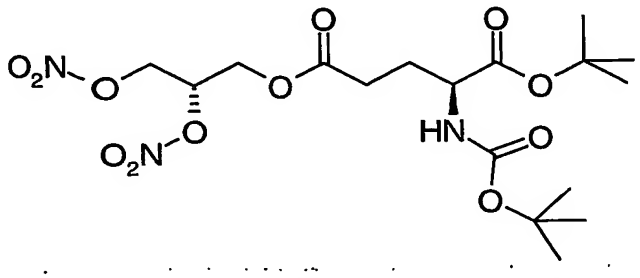


The product of Example 5b (1.92 g, 4.18 mmol) was taken up in a solution of HCl / EtOAc (10.1 g, 276 mmol) and stirred at room temperature overnight. Hexane was added to the solution and the resulting solid removed via filtration to give the title compound as a white solid (1.13 g, 80 % yield). Mp 137-140 °C: ^1H NMR (300 MHz,

$CDCl_3$) δ 8.39 (m, 1H), 4.58-4.56 (m, 2H), 4.38-4.33 (m, 1H), 3.96-3.92 (m, 1H), 3.83-3.78 (m, 1H), 3.42-3.38 (m, 1H), 3.01-2.96 (m, 1H), 2.57-2.51 (m, 2H), 2.07-1.91 (m, 2H), 1.76-1.62 (m, 5H), 1.24-0.95 (m, 2H). Mass spectrum (API-TIS) *m/z* 339(M+ 1).

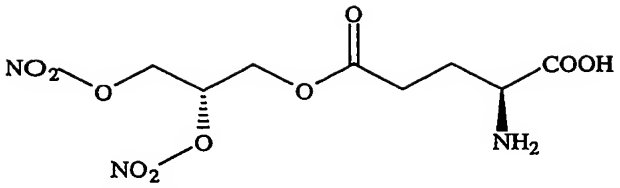
Example 6: (2S)-4-{[(2S)-2,3-Bis(nitrooxy)propyl]oxycarbonyl}-2-aminobutanoic acid; hydrochloride salt

6a. (2S)-2,3-Bis(nitrooxy)propyl tert-butyl (2S)-2-[(tert-butoxy) carbonylamino] pentane-1,5-dioate



To a solution of (4S)-4-((tert-butyl)oxycarbonyl)-4-((tert-butoxy) carbonylamino)butanoic acid (1.51 g, 5 mmol) and (2S)-2,3-bis(nitrooxy)propan-1-ol (prepared as described in US 2004/0024057, Example 51a) (0.91 g, 5 mmol) in anhydrous dichloromethane (25 mL) were added 1-ethyl-3-(3-dimethylaminopropyl) carbamide hydrochloride (EDAC) (0.96 g, 5 mmol) and dimethyl aminopyridine (DMAP, 0.61 g, 5 mmol) at room temperature under nitrogen atmosphere. The reaction mixture was stirred at room temperature overnight. The solvent was evaporated *in vacuo* and the residue was extracted with ethyl acetate, washed with water, brine, dried over sodium sulfate, filtered, and the organic extracts were evaporated. The product was purified by column chromatography over silica gel using 5% methanol in dichloromethane to give the title compound (1.01 g, 43% yield) as colorless thick oil. ^1H NMR (300 MHz, $CDCl_3$) δ 5.5-5.3 (m, 1H), 5.25-5.15 (m, 1H), 4.85-4.75 (dd, J = 12.9 and 3.6 Hz, 1H), 4.70-4.60 (dd, J = 13.0 and 4.9 Hz, 1H), 4.45-4.30 (m, 2H), 4.25-4.19 (m, 1H), 2.5-2.30 (m, 2H), 2.25-2.15 (m, 1H), 1.90-1.75 (m, 1H), 1.46 (s, 9H), 1.42 (s, 9H); ^{13}C NMR($CDCl_3$, 75 MHz) δ 172.1, 171.1, 155.4, 82.5, 79.9, 76.1, 68.6, 60.6, 52.9, 29.7, 28.2, 27.9. LRMS (APIMS) *m/z* 485 (M + NH_4), 468 (MH^+).

6b. (2S)-4-{[(2S)-2,3-Bis(nitrooxy)propyl]oxycarbonyl}-2-aminobutanoic acid; hydrochloride salt



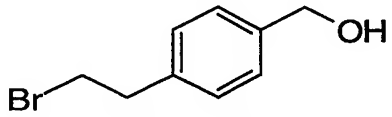
The title compound will be prepared from the product of Example 6a using the procedure for Example 5c.

Example 7: (2S)-2-Amino-4-[({4-[2-(nitrooxy)ethyl]phenyl}methyl) oxycarbonyl]butanoic acid, hydrochloride salt

7a. Methyl 4-(2-bromoethyl)benzoate

To a solution of 4-(2-bromoethyl)benzoic acid (2.75 g, 12 mmol) in methanol (100 mL), concentrated H_2SO_4 (0.5 mL) was added and the reaction mixture was refluxed overnight with a condenser attached with drying tube. Solvent was removed under reduced pressure and the residue was partitioned between ethyl acetate and water. Layers were separated and the aqueous layer was further extracted with ethyl acetate. The combined organic layers were washed with water, brine and dried (Na_2SO_4). Filtration and removal of solvent under reduced pressure yielded the desired product as colorless oil (2.87g, 98% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.99 (d, J = 8.3 Hz, 2H), 7.29 (d, J = 8.2 Hz, 2H), 3.91 (s, 3H), 3.60 (t, J = 3.7 Hz, 2H), 3.22 (t, J = 7.4 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.9, 144.0, 129.9, 128.9, 128.7, 52.1, 39.1, 32.1. LRMS (APIMS) *m/z* 245 $(M + H)^+$.

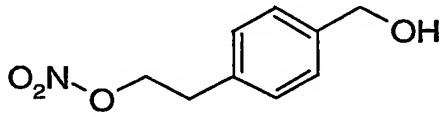
7b. [4-(2-Bromoethyl)phenyl]methan-1-ol



The product of Example 7a (2.87 g, 11.8 mmol) was dissolved in anhydrous THF (30 mL). To this solution DIBAL-H (1M in THF, 15 mL, 15 mmol) was slowly added and the reaction mixture was stirred overnight at room temperature under nitrogen atmosphere. The reaction was quenched with saturated aqueous NH_4Cl and acidified. THF was removed under reduced pressure, and the product was extracted with ethyl acetate. The combined organic layers were washed with water, brine, and dried (Na_2SO_4). Filtration and removal of solvent under reduced pressure yielded the desired product as colorless oil (1.51 g, 60% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ

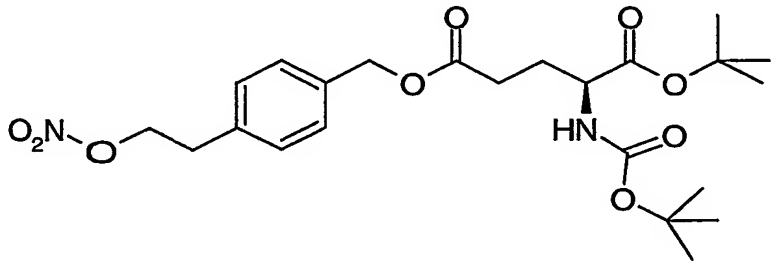
7.33 (d, J = 7.8 Hz, 2H), 7.21 (d, J = 8.1 Hz, 2H), 4.68 (d, J = 5.4 Hz, 2H) , 3.57 (t, J = 4.6 Hz, 2H), 3.17 (t, J = 7.5 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 139.5, 138.3, 128.9, 127.3, 65.1, 39.0, 32.9. LRMS (APIMS) *m/z* 234 $(M + NH_4)^+$.

7c. {4-[2-(Nitrooxy)ethyl]phenyl}methan-1-ol



To a solution of the product of Example 7b (1.5 g, 7 mmol) in anhydrous acetonitrile (30 mL), $AgNO_3$ (1.55 g, 9.1 mmol) was added and the reaction mixture was stirred overnight at room temperature under nitrogen atmosphere. More $AgNO_3$ (1.0 g) was added and the reaction mixture was heated to 70 °C for 2 hours. The solvent was removed under reduced pressure and the residue was partitioned between water and ethyl acetate and separated. The aqueous layer was further extracted with ethyl acetate and the combined organic layers were washed with water, brine and dried (Na_2SO_4). The residue was purified by silica gel flash column chromatography with 10% ethyl acetate in hexanes to yield the desired product as light yellow oil (1.16 g, 84% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.33 (d, J = 8.1 Hz, 2H), 7.22 (d, J = 8.1 Hz, 2H), 4.66 (d, J = 5.2 Hz, 2H) , 4.63 (t, J = 7.0 Hz, 2H), 3.02 (t, J = 7.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 139.8, 135.4, 129.1, 127.4, 73.3, 64.9, 33.0. LRMS (APIMS) *m/z* 412 $(2M + NH_4)^+$, 215 $(M + NH_4)^+$.

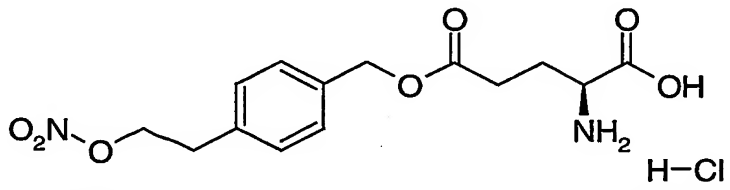
7d. tert-Butyl {4-[2-(nitrooxy)ethyl]phenyl}methyl (2S)-2-[(tert-butoxy) carbonylamino]pentane-1,5-dioate



The product of Example 7c (1.1 g, 5.6 mmol) and (4S)-4-((*tert*-butyl)oxycarbonyl)-4-((*tert*-butoxy)carbonylamino)butanoic acid (1.7 g, 5.6 mmol) were dissolved in anhydrous CH_2Cl_2 (25 mL). To this solution EDAC (1.07 g, 5.6 mmol) and DMAP (0.69 g, 5.6 mmol) were added and the reaction mixture was stirred

for 2 hours at room temperature under nitrogen atmostphere. Additional (4S)-4-((*tert*-butyl)oxycarbonyl)-4-((*tert*-butoxy)carbonylamino) butanoic acid (0.8 g, 2.6 mmol) was added and the reaction was stirred overnight. The reaction mixture was diluted with CH_2Cl_2 and washed with water, saturated aqueous $NaHCO_3$, brine and dried (Na_2SO_4). After filtration and removal of solvent under reduced pressure, the residue obtained was purified by silica gel flash column chromatography with 10% ethyl acetate in hexanes to give the pure product (2.42 g, 90% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.32 (d, J = 8.1 Hz, 2H), 7.22 (d, J = 8.1 Hz, 2H), 5.10 (s, 3H), 4.63 (t, J = 7.0 Hz, 2H), 3.02 (t, J = 7.0 Hz, 2H), 2.53-2.34 (m, 2H), 2.25-1.84 (m, 2H), 1.45 (s, 9H), 1.43 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.6, 171.3, 155.3, 136.1, 134.7, 129.1, 128.7, 82.2, 79.7, 73.1, 66.0, 53.3, 33.0, 30.2, 28.3, 28.0, 27.9. LRMS (APIMS) *m/z* 500 $(M + NH_4)^+$, 483 $(M + H)^+$.

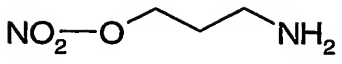
7e. (2S)-2-Amino-4-[({4-[2-(nitrooxy)ethyl]phenyl}methyl)oxycarbonyl]butanoic acid, hydrochloride salt



The product of Example 7d (1.01 g, 2.1 mmol) was dissolved in 4.4 M HCl in ethyl acetate (12 mL) and the reaction mixture was stirred at room temperature for 5 hours. During this time the hydrochloride salt precipitated out as a white solid. The reaction mixture was diluted with hexanes, filtered, washed with hexanes and dried under vacuum to yield the desired product as a white solid (0.72 g, 95% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.14 (br s, 3H), 7.15 (d, J = 8.5 Hz, 2H), 7.11 (d, J = 8.5 Hz, 2H), 4.90 (s, 2H), 4.56 (t, J = 6.6 Hz, 2H), 3.75 (t, J = 6.6 Hz, 2H), 2.83 (t, J = 6.6 Hz, 2H), 2.49-2.38 (m, 1H), 2.49-2.38 (m, 1H), 1.95-1.79 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.8, 170.7, 136.9, 134.6, 73.9, 65.7, 51.3, 32.1, 29.4, 25.3. LRMS (APIMS) *m/z* 653 (2M –HCl) + H)$^+$, 327 (M –HCl + H)$^+$.

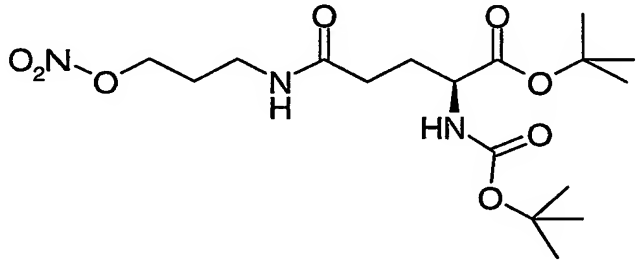
Example 8: (2S)-2-Amino-4-{N-[3-(nitrooxy)propyl]carbamoyl}butanoic acid, hydrochloride salt

8a. 3-(Nitrooxy)propylamine nitric acid salt



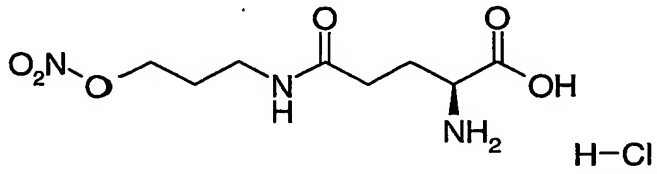
A solution of 3-amino-1-propanol (6.17 g, 82.2 mmol) was added, drop-wise, to an ice-cooled solution of fuming nitric acid (90%, 12 mL) in acetic anhydride (50 mL). The reaction was stirred in an ice-bath for 10 minutes and then at room temperature for 10 minutes. The solvent was evaporated under vacuum at 40 °C. The residue was stirred in Et_2O (200 mL) until the product precipitated. The mixture was filtered and the white crystalline solid was dried *in vacuo* to give the title compound (12.1 g, 80% yield). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 4.57 (br t, 2 H), 2.8 - 3.0 (m, 2H), 1.98-1.93 (m, 2H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ 70.9, 36.1, 24.5. Mass spectrum (API-TIS) *m/z* 121 $(MH)^+$.

8b. tert-Butyl (2S)-2-[(tert-butoxy)carbonylamino]-4-{N-[3-(nitrooxy)propyl] carbamoyl}butanoate



A solution of (4S)-4-((tert-butyl)oxycarbonyl)-4-((tert-butoxy)carbonylamino)-butanoic acid (3.05 g, 10.1 mmol), EDAC (2.53 g, 13.2 mmol), DMAP (0.15 g, 1.2 mmol), triethyl amine (2.8 mL, 20.1 mmol) and the product of Example 8a (2.04 g, 11.1 mmol) in CH_2Cl_2 (100 mL) was stirred at ambient temperature for 6 hours. The reaction mixture was partitioned between 3N HCl (50 mL) and CH_2Cl_2 (50 mL x 2). The combined organic extracts were washed with water, 2% $NaHCO_3$, 3N HCl, brine, dried over Na_2SO_4, filtered, concentrated and dried under vacuum to obtain the title compound as a sticky oil (4.03 g, 99% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.37 (brs, 1H), 5.49 (d, J = 8.1 Hz, 1H), 4.54 (t, J = 6.3 Hz, 2H), 4.2-4.0 (m, 1H), 3.37 (br q, 2H), 2.30 (t, J = 7.2 Hz, 2H), 2.2-1.8 (m, 4H), 1.47 (s, 9H), 1.44 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.4, 171.2, 155.8, 82.0, 79.7, 70.8, 53.4, 35.7, 32.3, 28.9, 28.0, 27.7, 26.7. Mass spectrum (API-TIS) *m/z* 406 $(MH)^+$.

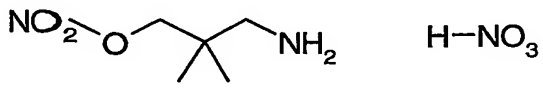
8c. (2S)-2-Amino-4-{N-[3-(nitrooxy)propyl]carbamoyl}butanoic acid, hydrochloride salt



A solution of Example 8b (4.03 g, 9.94 mmol) in Et_2O (50 mL) was treated with HCl/Et_2O (16% *wt.*, 37.9 g, 166.3 mmol) and stirred at ambient temperature for 40 hours. The resulted white solid was filtered, washed with Et_2O (50 mL) and dried under vacuum to obtain the title compound (2.7 g, 95% yield). Mp 57-60 °C. ^1H NMR (CD_3OD, 300 MHz) δ 4.57 (t, J = 6.3 Hz, 2H), 4.06 (br t, 1H), 3.33 (t, J = 6.6 Hz, 2H), 2.57-2.51 (m, 2H), 2.3-2.2 (m, 2H), 2.2-1.6 (m, 2H). ^{13}C NMR (CD_3OD, 75 MHz) δ 174.4, 171.4, 72.3, 53.5, 37.0, 32.5, 27.7, 27.1. Mass spectrum (API-TIS) *m/z* 250 $(MH)^+$.

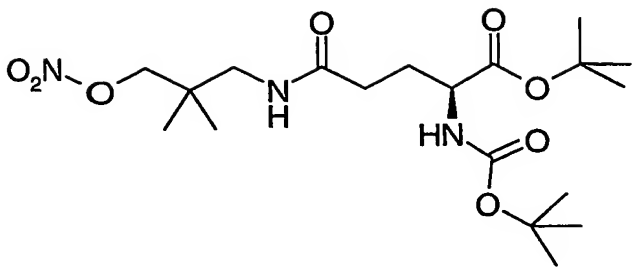
Example 9: (2S)-2-Amino-4-{N-[2,2-dimethyl-3-(nitrooxy)propyl]carbamoyl} butanoic acid, hydrochloride salt

9a. 2,2-Dimethyl-3-(nitrooxy)propylamine, nitric acid salt



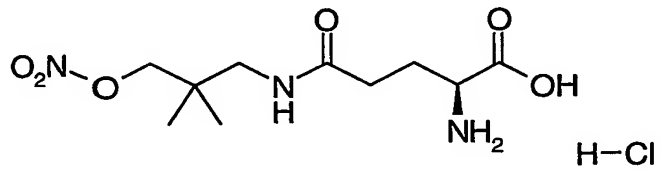
A solution of 3-amino-2,2-dimethylpropanol (6.0 g, 82.2 mmol) in EtOAc (40 mL) was added, drop-wise, to an ice-cooled solution of fuming nitric acid (90%, 8 mL) in acetic anhydride (50 mL). The reaction was stirred in an ice-bath for 10 minutes and an additional 10 minutes at room temperature. The solvent was evaporated under vacuum at 40 °C. The residue was stirred in Et_2O (200 mL) until the product precipitated. The mixture was filtered and the white solid was dried *in vacuo* to give the title compound (6.55 g, 53% yield). Mp 114-115 °C. ^1H NMR (DMSO-d_6, 300 MHz) δ 7.92 (br, 3H), 4.37 (s, 2H), 2.81 (br s, 2 H), 1.03 (s, 6H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ 77.5, 45.6, 33.3, 21.9. Mass spectrum (API-TIS) *m/z* 149 $(MH)^+$.

9b. tert-Butyl (2S)-2-[(tert-butoxy)carbonylamino]-4-{N-[2,2-dimethyl-3-(nitrooxy)propyl]carbamoyl}butanoate



A solution of (4S)-4-((tert-butyl)oxycarbonyl)-4-((tert-butoxy)carbonylamino)-butanoic acid (3.04 g, 10.0 mmol), 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride (2.67 g, 13.9 mmol), N,N-dimethylaminopyridine (0.18 g, 1.5 mmol), triethyl amine (2.8 mL, 20.1 mmol), and the product of Example 9a (2.48 g, 11.7 mmol) in CH_2Cl_2 (100 mL) was stirred at ambient temperature overnight. The reaction mixture was partitioned between 3N HCl (50 mL) and CH_2Cl_2 (50 mL x 2). The combined organic extracts were washed with water, 2% $NaHCO_3$, 3N HCl, brine, dried over Na_2SO_4, filtered, concentrated and dried under vacuum to obtain the title compound as a sticky oil (4.4 g, 99% yield). ^1H NMR ($CDCl_3$, 300 MHz) δ 7.37 (br, 1H), 5.44 (d, J = 8.2 Hz, 1H), 4.56 (s, 2H), 4.14 (br t, 1H), 3.3-3.1 (m, 2H), 2.31 (t, J = 6.8 Hz, 2H), 2.2-1.7 (m, 2H), 1.46 (s, 9H), 1.44 (s, 9H), 1.03 (s, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.5, 171.1, 156.1, 82.1, 79.8, 78.4, 53.2, 46.0, 35.3, 32.6, 29.7, 28.0, 27.7, 22.3. Mass spectrum (API-TIS) *m/z* 434 $(MH)^+$.

9c. (2S)-2-Amino-4-{N-[2,2-dimethyl-3-(nitrooxy)propyl]carbamoyl}butanoic acid, hydrochloride salt

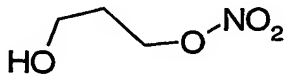


A solution of Example 9b (4.4 g, 9.94 mmol) in EtOAc (50 mL) was treated with HCl/EtOAc (7.9 g / 50 mL, 166.3 mmol) and stirred at ambient temperature for 36 hours. The resulted white solid was filtered, washed with Et_2O (50 mL) and dried under vacuum to obtain the title compound (2.83 g, 90% yield). Mp 65-68 °C. ^1H NMR (CD_3OD, 300 MHz) δ 4.03 (s, 2H), 3.82 (br t, 1H), 2.94 (d, J = 8.1 Hz, 2H), 2.33-2.30 (m, 2H), 2.1-1.8 (m, 2H), 0.77 (s, 6H). ^{13}C NMR (CD_3OD, 75 MHz) δ 174.6, 171.4, 79.6, 53.5, 47.1, 36.6, 32.5, 27.2, 22.8. Mass spectrum (API-TIS) *m/z* 278

$(M\text{-}Cl)^+$.

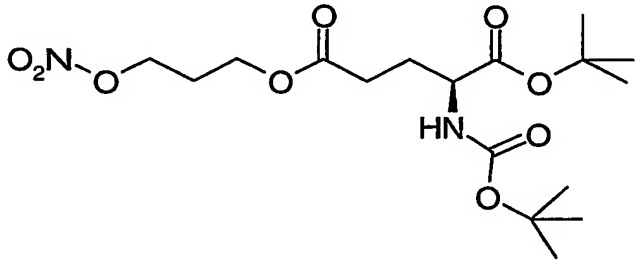
Example 10: (2S)-2-Amino-4-{[3-(nitrooxy)propyl]oxycarbonyl}butanoic acid, hydrochloride salt

10a. 3-(Nitrooxy)propan-1-ol



A solution of 3-bromo-1-propanol (5.42 g, 39.0 mmol) in acetonitrile (20 mL) was added to a solution of $AgNO_3$ (10.16 g, 59.8 mmol) in acetonitrile (50 mL) and stirred at room temperature for 24 hours. To the reaction mixture was added brine (350 mL) and stirred for 1 hour. The silver salts were filtered off through Celite and the filtrate was concentrated then extracted with Et_2O (200 mL x 3). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, concentrated and dried under vacuum to give the title compound (4.08 g, 86% yield, >95% purity). ^1H NMR ($CDCl_3$, 300 MHz) δ 4.61 (t, J = 6.4 Hz, 2H), 3.78 (t, J = 6.4 Hz, 2H), 1.99 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 70.3, 58.5, 29.5.

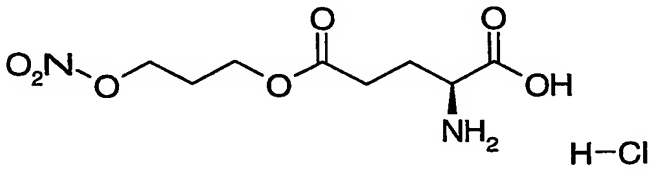
10b. tert-Butyl 3-(nitrooxy)propyl (2S)-2-[(tert-butoxy)carbonylamino]pentane-1,5-dioate



A solution of (4S)-4-((tert-butyl)oxycarbonyl)-4-((tert-butoxy)carbonylamino)-butanoic acid (3.03 g, 10.0 mmol), 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride (2.62 g, 13.7 mmol), N,N-dimethylaminopyridine (0.20 g, 1.7 mmol), triethyl amine (1.4 mL, 10.0 mmol), and Example 10a (1.24 g, 10.2 mmol) in CH_2Cl_2 (100 mL) was stirred at ambient temperature for 30 hours. The reaction mixture was partitioned between 3N HCl (50 mL) and CH_2Cl_2 (50 mL x 2). The combined organic extracts were washed with water, 2% $NaHCO_3$, 3N HCl, brine, dried over Na_2SO_4, filtered, concentrated and dried under vacuum. The product was separated by silica gel column chromatography eluting with EtOAc:hexane (2:3, Rf = 0.4) to give the title

compound as a sticky oil (3.56 g, 88% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.20-5.10 (br d, 1H), 4.56 (t, J = 6.3 Hz, 2H), 4.30-4.10 (m, 3H), 2.50-1.80 (m, 6H), 1.47 (s, 9H), 1.44 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.5, 171.2, 155.3, 82.1, 79.7, 69.8, 60.4, 35.2, 30.0, 28.2, 27.9, 27.8, 26.2. Mass spectrum (API-TIS) *m/z* 407 $(MH)^+$.

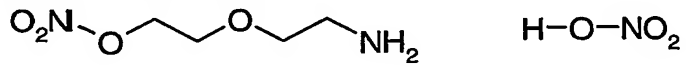
10c. (2S)-2-Amino-4-{[3-(nitrooxy)propyl]oxycarbonyl}butanoic acid, hydrochloride salt



A solution of Example 10b (3.56 g, 8.76 mmol) in EtOAc (50 mL) was treated with HCl/EtOAc (11.96 g / 50 mL, 327.7 mmol) and stirred at ambient temperature for 36 hours. The resulted white solid was filtered, washed with Et_2O (50 mL) and dried under vacuum to give the title compound (2.30 g, 92% yield). Mp 137-139 °C. ^{1}H NMR (CD_3OD, 300 MHz) δ 4.75 (t, J = 6.3 Hz, 2H), 4.38 (t, J = 6.3 Hz, 2H), 4.21 (t, J = 6.9 Hz, 1H), 2.81-2.75 (m, 2H), 2.5-2.2 (m, 4H). ^{13}C NMR (CD_3OD, 75 MHz) δ 173.6, 171.4, 71.6, 62.3, 53.1, 30.5, 27.4, 26.5. Mass spectrum (API-TIS) *m/z* 251 $(M-Cl)^+$.

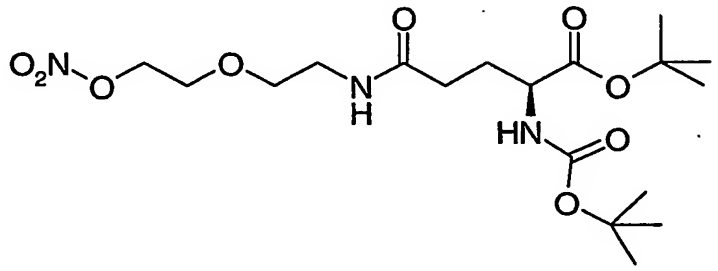
Example 11: (2S)-2-Amino-4-(N-{2-[2-(nitrooxy)ethoxy]ethyl}carbamoyl)butanoic acid, hydrochloride salt

11a. 2-[2-(Nitrooxy)ethoxy]ethylamine, nitric acid salt



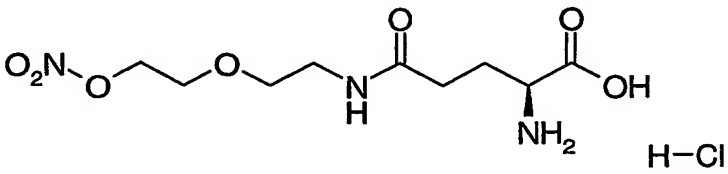
Fuming nitric acid (90%, 4.2 mL) was added to an ice-cooled of solution of 2-(2-aminoethoxy)ethanol (10.33 g, 98.2 mmol) in EtOAc (50 mL). To the resulted solution was added an ice-cooled solution of fuming nitric acid (90%, 8.4 mL) in acetic anhydride (20 mL). The reaction was stirred in an ice-bath for 10 minutes and an additional 20 minutes at room temperature. The solvent was evaporated under vacuum at 40 °C to give the title compound as a yellow oil (20.43 g, 98% yield). ^{1}H NMR (CD_3OD, 300 MHz) δ 4.7-4.6 (m, 2 H), 3.83 - 3.80 (m, 2H), 3.73-3.71 (m, 2H), 3.17-3.15 (br t, 2H). ^{13}C NMR (CD_3OD, 75 MHz) δ 73.5, 68.1, 67.9, 40.5. Mass spectrum (API-TIS) *m/z* 151 $(MH)^+$.

11b. tert-Butyl (2S)-2-[(tert-butoxy)carbonylamino]-4-(N-{2-[2-(nitrooxy) ethoxy]ethyl}carbamoyl)butanoate



To a solution of Example 10a (2.41 g, 11.3 mmol) in CH_2Cl_2 (30 mL) was added triethyl amine (1.6 mL, 1.4 mmol). The resulted solution was added to a solution of (4S)-4-((tert-butyl)oxycarbonyl)-4-((tert-butoxy)carbonylamino)-butanoic acid (3.11 g, 10.3 mmol), 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride (2.58 g, 13.5 mmol), N,N-dimethylaminopyridine (0.17 g, 1.4 mmol), and triethyl amine (3.2 mL, 23.0 mmol) in CH_2Cl_2 (30 mL) and stirred at ambient temperature for 4 hours. The reaction mixture was partitioned between 3N HCl (50 mL) and CH_2Cl_2 (50 mL x 2). The combined organic extracts were washed with water, saturated $NaHCO_3$, 3N HCl, brine, dried over Na_2SO_4, filtered, concentrated and dried under vacuum to give the title compound as a sticky oil (3.63 g, 81% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.60 (br, 1H), 5.35 (d, J = 8.1 Hz, 1H), 4.65-4.61 (m, 2H), 4.17-4.13 (m, 1H), 3.38-3.75 (m, 2H), 3.60-3.56 (m, 2H), 3.49-3.42 (m, 2H), 232-1.85 (m, 4H), 1.49 (s, 9H), 1.46 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.2, 171.3, 155.7, 82.0, 79.6, 71.8, 69.8, 66.7, 53.4, 38.9, 32.4, 29.1, 28.1, 27.8. Mass spectrum (API-TIS) *m/z* 436 $(MH)^+$.

11c. (2S)-2-Amino-4-(N-{2-[2-(nitrooxy)ethoxy]ethyl}carbamoyl)butanoic acid, hydrochloride salt

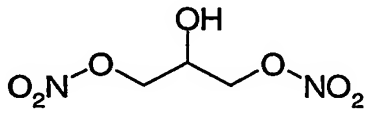


A solution of Example 11b (3.63 g, 8.3 mmol) in EtOAc (20 mL) was treated with HCl/EtOAc (9.26 g / 50 mL, 250 mmol) and stirred at ambient temperature for 24 hours. The reaction mixture was concentrated and dried under vacuum to give the title compound as a sticky oil (2.03 g, 77% yield). ^{1}H NMR (CD_3OD, 300 MHz) δ 4.70-

4.65 (m, 2H), 4.20-4.00 (m, 1H), 3.81-2.78 (m, 2H), 3.62-3.58 (m, 2H), 3.49-3.37 (m, 2H), 2.70-2.50 (m, 2H), 2.40-2.10 (m, 2H). ^{13}C NMR (CD_3OD, 75 MHz) δ 174.4, 171.3, 73.7, 70.2, 67.9, 53.5, 40.3, 32.3, 27.1. Mass spectrum (API-TIS) *m/z* 280 $(MH)^+$.

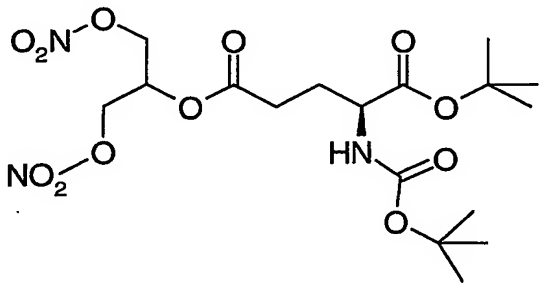
Example 12: (2S)-2-Aamino-4-({2-(nitrooxy)-1-[(nitrooxy)methyl]ethyl} oxycarbonyl)butanoic acid, hydrochloride salt

12a. 1,3-Bis(nitrooxy)propan-2-ol



A solution of 1,3-dibromo-2-propanol (32.48 g, 0.15 mol) and $AgNO_3$ (62.49 g, 0.37 mol) in acetonitrile (150 mL) was stirred at room temperature overnight and additional 8 hours at 75° C. To the reaction mixture was added brine (150 mL) and stirred for 1 hour. The silver salts were filtered off through Celite and the filtrate was concentrated then extracted with CH_2Cl_2 (150 mL x 3). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The product was separated by silica gel column chromatography eluting with MeOH:$CHCl_3$ (gradient from 0 to 3%, R*f* = 0.1 in 0.5% MeOH) to give the title compound as a clear oil (14.1 g, 52% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.65-4.50 (m, 4H), 4.37-4.28 (m, 1H), 3.35-3.33 (br, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 72.4 (sym overlapping), 65.3. Mass spectrum (API-TIS) *m/e* 241 $(M+OAc)^-$.

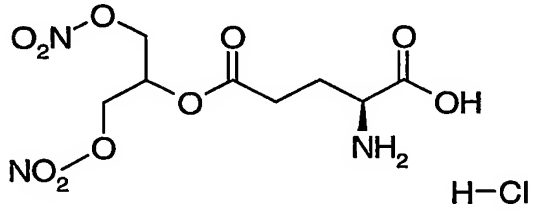
12b. tert-Butyl 2-(nitrooxy)-1-[(nitrooxy)methyl]ethyl (2S)-2-[(tert-butoxy) carbonylamino]pentane-1,5-dioate



A solution of (4S)-4-((tert-butyl)oxycarbonyl)-4-((tert-butoxy)carbonylamino)-butanoic acid (3.04 g, 9.89 mmol), 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide

hydrochloride (2.52 g, 13.1 mmol), N,N-dimethylaminopyridine (0.26 g, 2.1 mmol), triethyl amine (1.4 mL, 10.0 mmol), and the product of Example 12a (1.80 g, 9.89 mmol) in CH_2Cl_2 (60 mL) was stirred at ambient temperature overnight. The reaction mixture was partitioned between 3N HCl (50 mL) and CH_2Cl_2 (50 mL x 2). The combined organic extracts were washed with water, 2% $NaHCO_3$, 3N HCl, brine, dried over Na_2SO_4, filtered, concentrated and dried under vacuum to give the title compound as a sticky oil (4.45 g, 96% yield, >95% purity). The product was used in the next step without purification. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.45-5.40 (m, 1H), 5.22 (br d, J = 8.0 Hz, 1H), 4.80-4.55 (m, 4H), 4.3-4.15 (br q, 1H), 2.55-2.35 (m, 2H), 2.30-1.80 (m, 2H), 1.49 (s, 9H), 1.44 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.5, 171.0, 155.3, 82.1, 79.6, 69.5, 66.2, 52.8, 29.6, 28.0, 27.7. Mass spectrum (API-TIS) *m/z* 468 $(MH)^+$.

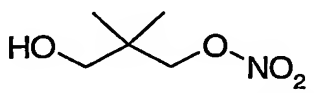
12c. (2S)-2-Amino-4-({2-(nitrooxy)-1-[(nitrooxy)methyl]ethyl} oxycarbonyl) butanoic acid, hydrochloride salt



A solution of the product of Example 12b (4.45 g, 9.52 mmol) in EtOAc (50 mL) was treated with HCl/EtOAc (9.41 g / 50 mL, 0.26 mol) and stirred at ambient temperature for 20 hours. The resulted white solid was filtered, washed with hexane (50 mL) and dried under vacuum to give the title compound (2.94 g, 89% yield). Mp 139 °C (dec.). ^{1}H NMR (300 MHz, CD_3OD) δ 5.35-5.25 (m, 1H), 4.68-4.62 (m, 2H), 4.50-4.32 (m, 2H), 3.84 (t, J = 6.7 Hz, 1 H), 2.50-2.40 (m, 2H), 2.10-2.00 (m, 2H). ^{13}C NMR (75 MHz, CD_3OD) δ 172.7, 171.3, 71.5, 68.4, 52.9, 30.4, 26.4. Mass spectrum (API-TIS) *m/z* 312 $(MH)^+$.

Example 13: (2S)-2-amino-4-{[2,2-dimethyl-3-(nitrooxy)propyl]oxycarbonyl} butanoic acid, hydrochloride salt

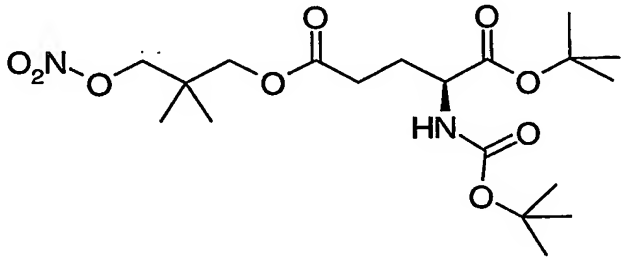
13a. 2,2-Dimethyl-3-(nitrooxy)propan-1-ol



Nitric acid (90%, 12.3 mL, 0.26 mol) was added to acetic anhydride (37 mL) at

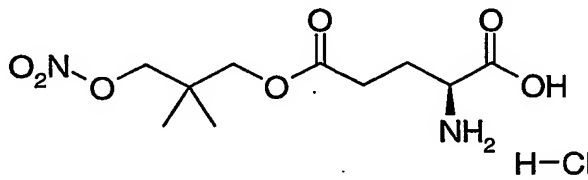
0 °C with stirring. After 15 minutes, a cold (0 °C) solution of neopentyl glycol (25 g, 0.24 mol) in THF (150 mL) was added in one portion. The mixture was allowed to warm to room temperature in 35 minutes, diluted with EtOAc, and washed with aqueous Na_2CO_3 three times. The organic layer was dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The residue was purified by silica gel column chromatography (1:9 and then 1:5 EtOAc:Hexane) to give the title compound (31.5 g, 88% yield) as a slightly yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.27 (s, 2H), 3.37 (s, 2H), 2.83 (br, 1H), 0.94 (s, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 77.64, 67.96, 35.94, 21.25.

13b. tert-butyl 2,2-dimethyl-3-(nitrooxy)propyl (2S)-2-[(tert-butoxy)carbonylamino] pentane-1,5-dioate



The product of Example 13a was treated following the procedure of Example 12b to give a crude product that was separated by silica gel column chromatography eluting with EtOAc:hexane (gradient from 1:5 to 1:3, R*f* = 0.4 in 1:3) to give the title compound as a sticky oil (3.01 g, 71% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.37 (br d, *J* = 8.3 Hz, 1H), 4.31 (s, 2H), 4.30-4.15 (br q, 1H), 4.00-3.85 (m, 2H), 2.50-2.35 (m, 2H), 2.2-1.85 (m, 2H), 1.47 (s, 9H), 1.44 (s, 9H), 1.05 (s, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.0, 170.9, 155.0, 81.5, 79.1, 77.0, 68.5, 52.9, 34.4, 29.7, 27.8, 27.5, 21.3. Mass spectrum (API-TIS) *m/z* 435 $(MH)^+$.

13c. (2S)-2-Amino-4-{[2,2-dimethyl-3-(nitrooxy)propyl]oxycarbonyl}butanoic acid, hydrochloride salt

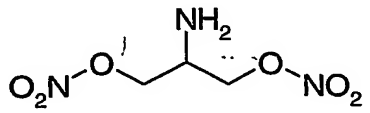


A solution of Example 13b (3.01 g, 6.93 mmol) in EtOAc (50 mL) was treated

with HCl/EtOAc (17.9% *wt.*, 39.9g, 0.20 mol) and stirred at ambient temperature overnight. The resulted white solid was filtered, washed with hexane (50 mL) and dried under vacuum to give the title compound (1.87 g, 86% yield). Mp 132-135 °C. ^{1}H NMR (CD_3OD, 300 MHz) δ 4.52 (s, 2H), 4.22 (t, J = 6.7 Hz, 1H), 4.13 (d, J = 3.8 Hz, 2H), 2.85-2.75 (m, 2H), 2.45-2.35 (m, 2H), 1.21 (s, 6 H). ^{13}C NMR (75 MHz, CD_3OD) δ 173.4, 171.3, 78.7, 70.4, 53.1, 35.8, 30.4, 26.5, 21.9. Mass spectrum (API-TIS) *m/z* 279 $(MHI)^+$.

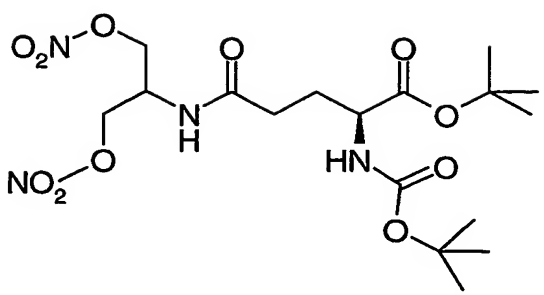
Example 14: tert-Butyl (2S)-2-[(tert-butoxy)carbonylamino]-4-(N-{2-(nitrooxy)-1-[(nitrooxy)methyl]ethyl}carbamoyl)butanoate

14a. 1,3-Bis(nitrooxy)prop-2-ylamine



Furning nitric acid (90%, 4.02 mL) was added to an ice-cooled solution of serinol (8.51 g, 93.4 mmol) in EtOAc (30 mL) and acetonitrile (10 mL) and the resulted mixture was concentrated and dried under vacuum. The residue was dissolved in acetic acid (30 mL) and was added to an ice-cooled solution of fuming nitric acid (90%, 12.0 mL) in acetic anhydride (25 mL). The reaction was stirred in an ice-bath for 5 minutes and additional 5 minutes at room temperature. The solvent was evaporated under vacuum. The residue was dissolved in water (50 mL), make basic with 2N NaOH (50 mL), and extracted with $CHCl_3$ (150 mL x 3). The combined organic extracts were washed with water, brine, dried over Na_2SO_4, filtered, concentrated and dried under vacuum to give the title compound as a yellow oil (12.91 g, 76% yield, 90% purity). The product was used in the next step without purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.60-4.30 (m, 4H), 3.55-3.45 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 73.4, 47.1. Mass spectrum (API-TIS) *m/z* 182 $(MH)^+$.

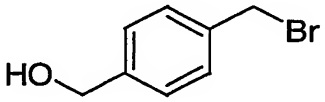
14b. tert-Butyl (2S)-2-[(tert-butoxy)carbonylamino]-4-(N-{2-(nitrooxy)-1-[(nitrooxy)methyl]ethyl}carbamoyl)butanoate



A solution of (4S)-4-((tert-butyl)oxycarbonyl)-4-((tert-butoxy)carbonylamino)-butanoic acid (3.18 g, 10.5 mmol), 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride (2.57 g, 13.4 mmol), N,N-dimethylaminopyridine (0.25 g, 2.1 mmol), triethyl amine (1.4 mL, 10.0 mmol), and Example 14a (2.0 g, 11.0 mmol) in CH_2Cl_2 (60 mL) was stirred at ambient temperature overnight. The reaction mixture was partitioned between 3N HCl (50 mL) and CH_2Cl_2 (50 mL x 2). The combined organic extracts were washed with water, 2% $NaHCO_3$, 3N HCl, brine, dried over Na_2SO_4, filtered, concentrated and dried under vacuum. Attempt to purify the crude material by silica gel chromatography resulted partial decomposition. Mass spectrum (API-TIS) *m/z* 467 $(MH)^+$.

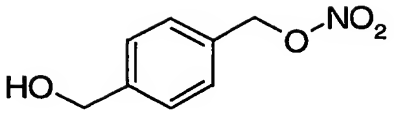
Example 15: (2S)-2-Amino-4-[({4-[(nitrooxy)methyl]phenyl}methyl) oxycarbonyl]butanoic acid, hydrochloride salt

15a. (4-(Bromomethyl)phenyl)methan-1-ol



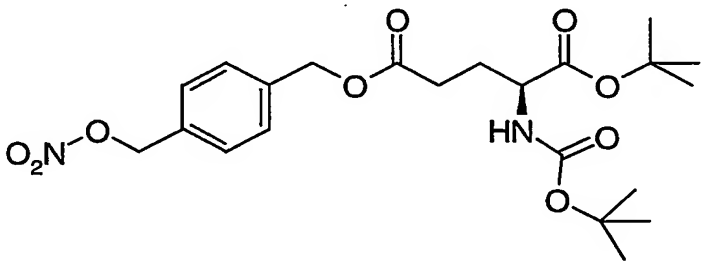
A solution of BH_3•SMe_2 in THF (2M, 24 mL, 48 mmol) was added, slowly, to 4-(bromomethyl)benzoic acid (10.11 g, 47 mmol) in THF (200 mL) and CH_2Cl_2 (50 mL) and stirred at ambient temperature overnight. To the reaction was added methanol (10 mL) and stirred for 30 minutes then evaporated to dryness. To the resulted material was added CH_2Cl_2 (100 mL) and the insoluble material was filtered. The filtrate was concentrated and dried under vacuum to give a yellow solid (6.48 g, 69% yield). The crudely purified material contained some starting material was used in the next step without further purification. ^1H NMR (300 MHz, $CDCl_3$) δ 7.35-7.3 (m, 4H), 4.58 (s, 2H), 4.54 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.0, 138.6, 130.2, 128.2, 64.7, 33.9.

15b. (4-((Nitrooxy)methyl)phenyl)methan-1-ol



A solution of Example 15a (5.88 g, 29.3 mmol) and $AgNO_3$ (7.0 g, 41.2 mmol) in acetonitrile (100 mL) was stirred at ambient temperature overnight then at 60 °C for 2 hours. To the reaction mixture was added brine (10 mL) and stirred for 1 hour. The silver salts were filtered off through Celite and the filtrate was concentrated then extracted with CH_2Cl_2 (100mL x 2). The combined organic extracts were washed with 5% $NaHCO_3$, 3N HCl, brine, dried over Na_2SO_4, filtered, concentrated and dried under vacuum to give the title compound as a light yellow oil (3.38 g, 63% yield). ^1H NMR (300 MHz, $CDCl_3$) δ 7.40-7.25 (m, 4H), 5.37 (s, 2H), 4.55 (s, 2H), 3.36 (br, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.1, 131.0, 129.2, 127.0, 74.5, 64.1. Mass spectrum (API-TIS) *m/e* 242 $(M+OAc)^-$.

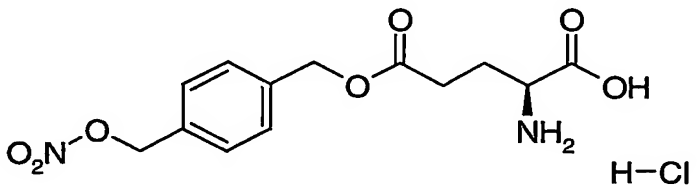
15c. tert-Butyl {4-[(nitrooxy)methyl]phenyl}methyl (2S)-2-[(tert-butoxy) carbonylamino]pentane-1,5-dioate



A solution of (4S)-4-((tert-butyl)oxycarbonyl)-4-((tert-butoxy)carbonylamino)-butanoic acid (3.16 g, 10.4 mmol), 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride (2.77 g, 14.5 mmol), N,N-dimethylaminopyridine (0.27 g, 2.2 mmol), triethyl amine (1.4 mL, 10.0 mmol), and Example 15b (1.82 g, 9.94 mmol) in CH_2Cl_2 (50 mL) was stirred at ambient temperature overnight. The reaction mixture was partitioned between 3N HCl (50 mL) and CH_2Cl_2 (50 mL x 2). The combined organic extracts were washed with water, 5% $NaHCO_3$, 3N HCl, brine, dried over Na_2SO_4, filtered, concentrated and dried under vacuum. The product was separated by silica gel column chromatography eluting with EtOAc:hexane (1:4, $Rf = 0.18$) to give the title compound as a sticky oil (1.3 g, 28% yield). ^1H NMR (300 MHz, $CDCl_3$) δ 7.37 (d, J = 7.6 Hz, 4H) 5.41 (s, 2H), 5.27 (br d, J = 8.0 Hz, 1H), 5.13 (d, J = 1.8 Hz, 2H), 4.30-

4.15 (br q, 1H), 2.50-2.25 (m, 2H), 2.20-1.80 (m, 2H), 1.45 (s, 9H), 1.43 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 170.0, 155.2, 137.1, 132.0, 129.0, 128.2, 81.8, 79.3, 74.1, 65.4, 53.1, 30.0, 28.0, 27.6. Mass spectrum (API-TIS) *m/z* 469 $(MH)^+$.

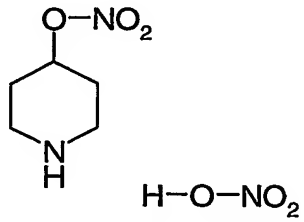
15d. (2S)-2-Amino-4-[({4-[(nitrooxy)methyl]phenyl}methyl)oxycarbonyl]butanoic acid, hydrochloride salt



A solution of Example 15c (1.3 g, 2.77 mmol) in EtOAc (25 mL) was treated with HCl/EtOAc (17.9% *wt.*, 12.5 g, 61.5 mmol) and stirred at ambient temperature overnight. The resulted white solid was filtered, washed with hexane (50 mL) and dried under vacuum to give the title compound (0.83 g, 86% yield). Mp 135-138°C. ^1H NMR (300 MHz, CD_3OD) δ 7.45-7.40 (m, 4H), 5.49 (s, 2H), 5.17 (s, 2H), 4.08 (t, *J* = 6.6 Hz, 1H), 2.69-2.64 (m, 2H), 2.29-2.18 (m, 2H). ^{13}C NMR (75 MHz, CD_3OD) δ 173.4, 171.3, 138.7, 134.2, 130.4, 129.6, 75.7, 67.1, 53.1, 30.6, 26.6. Mass spectrum (API-TIS) *m/z* 313 $(MH)^+$.

Example 16: (2S)-2-Amino-5-[4-(nitrooxy)piperidyl]-5-oxopentanoic acid, hydrochloride salt

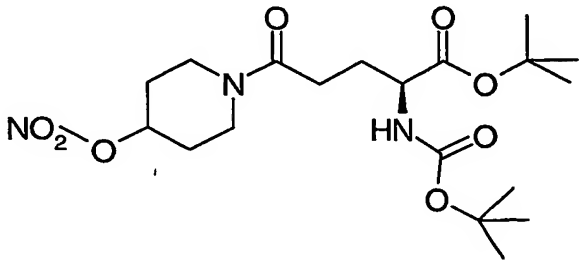
16a. Nitrooxy-4-piperidyl, nitric acid salt



4-Hydroxypiperidine (2.2 g, 22 mmol) was dissolved in ethyl acetate (125 mL) and the resulting solution was cooled to 0 °C. In a separate flask acetic anhydride (17 mL) and 90% nitric acid (4.2 mL) were mixed together at 0 °C and this nitrating mixture was then added at 0 °C to the above mixture. The resulting mixture was then stirred at 0 °C for 10 minutes and then at room temperature for 30 minutes. The reaction mixture was then concentrated in *vacuo* to give the title compound in quantitative yield as a white solid. Mp 138-141 °C. ^1H NMR (d_6-DMSO, 300 MHz) δ

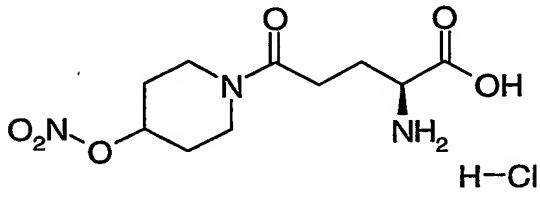
8.69-8.61 (m, 2H), 5.26 (m, 1H), 3.19 (m, 4H), 1.86 (m, 2H); ^{13}C NMR (d_6-DMSO, 75 MHz) δ 77.0, 41.1 (2 x C), 26.1 (2 x C); LRMS (APIMS) *m/z* 147 $((MH)^+$.

16b. *tert*-Butyl (2S)-2-[(tert-butoxy)carbonylamino]-5-[4-(nitrooxy)piperidyl]-5-oxopentanoate



To a suspension of the product of Example 16a (2.1 g, 10 mmol) in anhydrous CH_2Cl_2 (20 mL), triethylamine (1.4 mL, 9.8 mmol) was added. After addition of EDAC (0.48 g, 2.5 mmol), a solution of (4S)-4-((*tert*-butyl)oxycarbonyl)-4-((*tert*-butoxy)carbonylamino)butanoic acid (0.76 g, 2.5 mmmol) in anhydrous CH_2Cl_2 (15 mL) was slowly added and the reaction mixture was stirred for 1 hr at room temperature under nitrogen atmosphere. The reaction mixture was diluted with CH_2Cl_2, washed with water, brine and dried (Na_2SO_4). After filtration and removal of the solvent under reduced pressure, the residue was purified by silica gel flash column chromatography with 20% ethyl acetate in hexanes to give the title compound as a thick oil (0.62 g, 58% yield). ^1H NMR ($CDCl_3$, 300 MHz) δ 5.20-5.11 (m, 2H), 4.15-4.12 (m, 1H), 3.87-3.83 (m, 1H), 3.67-3.61 (m, 1H), 3.53-3.35 (m, 2H), 2.47-2.28 (m, 2H), 2.17-2.14 (m, 1H), 2.00-1.94 (m, 3H), 1.79-1.65 (m, 2H), 1.44 (s, 9H), 1.41 (s, 9H). LRMS (APIMS) *m/z* 880 $(2M + NH_4)^+$, 432 $(M + H)^+$.

16c. (2S)-2-Amino-5-[4-(nitrooxy)piperidyl]-5-oxopentanoic acid, hydrochloride salt

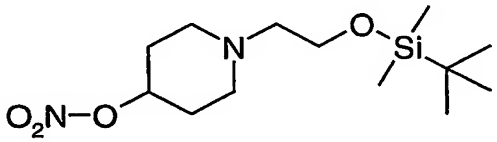


The product of Example 16b (0.58 g, 1.3 mmol) was dissolved in 4.4 M HCl in ethyl acetate (8 mL) and the resulting solution was stirred at room temperature for 1 hour during which the hydrochloride salt was precipitated as a white solid. The reaction mixture was diluted with hexanes, filtered, washed with hexanes and dried

under vacuum to yield the title compound as a white foam (0.24 g, 59% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.41 (br s, 3H), 4.15 (s, 1H), 2.89-2.70 (m, 2H), 2.68-2.51 (m, 1H), 2.25-2.15 (m, 2H), 1.55-1.32 (m, 2H), 1.12-0.68 (m, 4H), 0.57-0.33 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.0, 169.6, 80.1, 51.8, 42.0, 38.5, 29.2, 28.6, 28.3, 25.7. LRMS (APIMS) *m/z* 551 $(2(M - HCl) + H)^+$, 276 $(M - HCl + H)^+$.

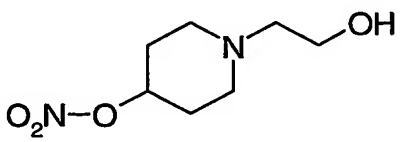
Example 17: (2S)-2-Amino-4-({2-[4-(nitrooxy)piperidyl]ethyl}oxycarbonyl) butanoic acid, hydrochloride salt

17a. Nitrooxy{1-[2-(1,1,2,2-tetramethyl-1-silapropoxy)ethyl](4-piperidyl)}



To a solution of the product of Example of 16a (2.1 g, 10 mmol) in anhydrous DMF (20 mL) were added successively K_2CO_3 (13.8 g, 100 mmol), triethylamine (1.4 mL, 10 mmol) and (2-bromoethoxy)-*tert*-butyldimethylsilane (2.1 mL, 10 mmol). The reaction mixture was stirred vigorously at room temperature overnight under a nitrogen atmosphere. The solvent was removed under vacuum and the residue was partitioned between water and ethyl acetate and the aqueous layer was further extracted with ethyl acetate. The combined organic layers were washed with brine and dried (Na_2SO_4). After filtration and removal of solvent under reduced pressure, the residue was purified by silica gel flash column chromatography using 10% ethyl acetate in hexanes to yield the title compound as a yellow oil (1.87 g, 61% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.94 (m, J = 4.2 Hz, 1H), 3.72 (t, J = 7.0 Hz, 2H), 2.81-2.75 (m, 2H), 2.52 (t, J = 6.2 Hz, 2H), 2.42-2.34 (m, 2H), 2.04-1.95 (m, 2H) 1.84-1.73 (m, 2H). 0.88 (s, 9H), 0.04 (s, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 79.8, 61.4, 60.1, 51.0, 29.3, 25.9, 18.3, 5.5. LRMS (APIMS) *m/z* 305 $(M + H)^+$.

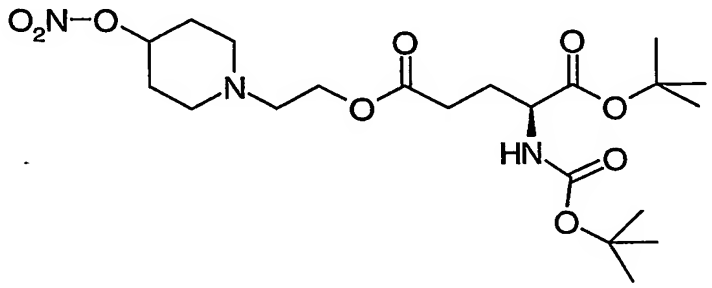
17b. 2-[4-(nitrooxy)piperidyl]ethan-1-ol



To a solution of the product of Example 17a (2.56 g, 8.4 mmol) in anhydrous THF (10 mL) was added tetrabutylammonium fluoride (1M in THF, 12 mL) and the

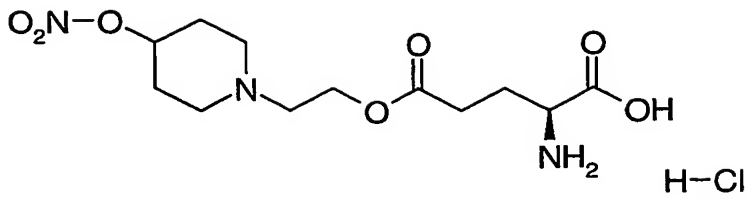
reaction mixture was stirred for 3 days at room temperature under a nitrogen atmosphere. The solvent was removed under reduced pressure and the residue was purified by silica gel flash column chromatography using CH_2Cl_2 to give the title compound as a pale yellow oil (1.13 g, 99% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.00 (m, J = 4.0 Hz, 1H), 3.72 (t, J = 7.0 Hz, 2H), 2.79-2.72 (m, 2H), 2.55 (t, J = 5.4 Hz, 2H), 2.45-2.37 (m, 2H), 2.06-2.02 (m, 3H) 1.85-1.75 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 79.4, 59.0, 58.0, 50.1, 29.2. LRMS (APIMS) *m/z* 191 $(M + H)^+$.

17c. *tert*-butyl 2-[4-(nitrooxy)piperidyl]ethyl (2S)-2-[(tert-butoxy)carbonylamino] pentane-1,5-dioate



The product of Example 17b (0.56 g, 3 mmol) was dissolved in anhydrous CH_2Cl_2 (10 mL). To this solution EDAC (0.57g, 3 mmol) was added and while stirring, (4S)-4-((*tert*-butyl)oxycarbonyl)-4-((*tert*-butoxy)carbonylamino)butanoic acid (900 mg, 3 mmol) in anhydrous CH_2Cl_2 (10 mL) was slowly added. The reaction mixture was further stirred at room temperature for 2.5 hours. The reaction mixture was then diluted with CH_2Cl_2 and then washed with water, brine and dried (Na_2SO_4). After filtration and the removal of solvent under reduced pressure, the residue was purified by silica gel flash column chromatography using 30% ethyl acetate in hexanes to yield the title compound as a colorless oil (0.47 g, 33% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.23 (d, J = 8.0 Hz, 1H), 4.97 (m, J = 4.0 Hz, 1H), 4.27-4.18 (m, 2H), 2.78-2.73 (m, 2H), 2.63 (q, J = 5.4 Hz, 2H), 2.43-2.35 (m, 4H), 2.24-1.76 (m, 7H), 1.46 (s, 9H), 1.43 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.7, 171.3, 155.4, 82.1, 79.8, 79.4, 61.7, 60.3, 56.2, 53.3, 50.4, 30.4, 29.0, 28.3, 27.9, 21.0, 14.1. LRMS (APIMS) *m/z* 476 $(M + H)^+$.

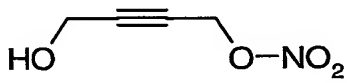
17d. (2S)-2-Amino-4-({2-[4-(nitrooxy)piperidyl]ethyl}oxycarbonyl)butanoic acid, hydrochloride salt



The product of Example 17c (0.44 g, 0.9 mmol) was dissolved in 4.4 M HCl in ethyl acetate, (6 mL) and the resulting solution was stirred overnight at room temperature. The hydrochloride salt precipitated as a solid and the reaction mixture was diluted with hexanes, solvent was decanted, and the solid product was washed with hexanes and dried under vacuum to give the title compound (360 mg, 100% yield). LRMS (APIMS) *m/z* 320 $(M - HCl + H)^+$.

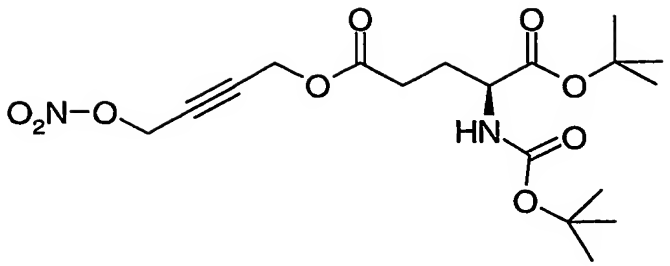
Example 18: (2S)-2-Amino-4-{[4-(nitrooxy)but-2-ynyl]oxycarbonyl}butanoic acid, hydrochloride salt

18a. 4-(Nitrooxy)but-2-yn-1-ol



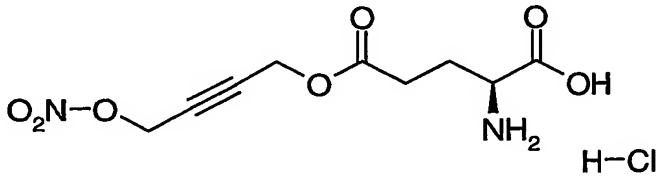
Nitric acid (90%, 14.3 mL, 0.30 mol) was added to acetic anhydride (40 mL) at 0 °C with stirring. After 10 minutes, a cold (0 °C) solution of 2-butyne-1,4-diol (17.22 g, 0.20 mol) in THF (200 mL) was added in one portion. The mixture was allowed to warm to room temperature in 30 minutes, diluted with EtOAc, and washed with aqueous Na_2CO_3 three times. The organic layer was dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The residue was purified by column chromatography (silica gel, 1:5 to 1:0 of EtOAc:Hexane gradient eluent) to give the title compound (16.3 g, 62% yield) as a slightly yellow liquid. ^1H NMR (300 MHz, $CDCl_3$) δ 5.08 (s, 2H), 4.32 (t, J = 1.8 Hz, 2H), 3.22 (br, d, J = 1.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 87.2, 76.4, 60.3, 50.4.

18b. tert-Butyl 4-(nitrooxy)but-2-ynyl (2S)-2-[(tert-butoxy)carbonylamino]pentane-1,5-dioate



A solution of (4S)-4-((tert-butyl)oxycarbonyl)-4-((tert-butoxy)carbonylamino)-butanoic acid (3.20 g, 10.6 mmol), 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride (2.77 g, 14.5 mmol), N,N-dimethylaminopyridine (0.30 g, 2.4 mmol) and Example 18a (1.35 g, 10.3 mmol) in CH_2Cl_2 (60 mL) was stirred at ambient temperature overnight. The reaction mixture was partitioned between 3N HCl (50 mL) and CH_2Cl_2 (50 mL x 2). The combined organic extracts were washed with water, 5% Na_2CO_3, 3N HCl, brine, dried over Na_2SO_4, filtered, concentrated and dried under vacuum. The product was separated by silica gel column chromatography eluting with EtOAc:hexane (1:4, R*f* = 0.15) to give the title compound as a clear oil (2.34 g, 53% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.34 (br d, 1H), 5.08 (s, 2H), 4.75-4.74 (m, 2H), 4.25-4.1 (br q, 1H), 2.55-2.45 (m, 2H), 2.3-1.90 (m, 2H), 1.47 (s, 9H), 1.44 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5, 170.9, 155.0, 82.8, 81.7, 79.2, 77.5, 59.8, 52.9, 51.5, 29.6, 27.9, 27.5, 27.4. Mass spectrum (API-TIS) *m/z* 417 $(MH)^+$.

18c. (2S)-2-amino-4-{[4-(nitrooxy)but-2-ynyl]oxycarbonyl}butanoic acid, hydrochloride salt

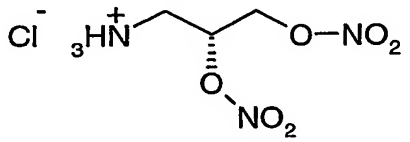


A solution of the product of Example 18b (2.34 g, 5.62 mmol) in EtOAc (40 mL) was treated with HCl/Et_2O (15.9 *wt.*, 34.56 g, 150.5 mmol) and stirred at ambient temperature overnight. The resulted white solid was filtered, washed with hexane (50 mL) and dried under vacuum to give the title compound as a white solid (12.9 g, 78% yield). Mp 107-110°C. ^{1}H NMR (300 MHz, CD_3OD) δ 5.18 (br s, 2H), 4.83-4.81 (m, 1H), 4.08 (t, *J* = 6.6 Hz, 1H), 2.75-2.60 (m, 2H), 2.32-2.15 (m, 2H). ^{13}C NMR (75 MHz, CD_3OD) δ 172.8, 171.3, 83.9, 79.3, 61.4, 53.0, 30.3, 26.4. Mass spectrum (API-

TIS) *m/z* 261 $(M\text{-}Cl)^+$.

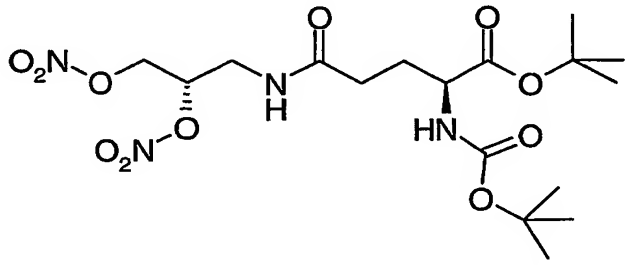
Example 19: (2S)-4-{N-[(2S)-2,3-Bis(nitrooxy)propyl]carbamoyl}-2-aminobutanoic acid, hydrochloride salt

19a. (2R)-2,3-Bis(nitrooxy)propylamine, hydrochloride salt



Fuming nitric acid (4.5 mL, 113.7 mmol) and acetic anhydride (Aldrich, Wisconsin, U.S., 17.2 mL, 181.9 mmol) were combined at 0 °C and stirred for 15 minutes. The mixture was then added to a solution of (R)-3-amino-1,2-propandiol (Aldrich, Wisconsin, U.S., 2.1 g, 22.7 mmol) and fuming nitric acid (2.7 mL, 68.2 mmol) in EtOAc (10 mL) cooled to 0 °C, and the resulting mixture stirred at 0 °C for 3 hours. The solvent was removed under reduced pressure and the resulting residue triturated in ether to give the title compound (1.1 g, 23% yield) as a solid which was collected via filtration: ^1H NMR (300 MHz, $CDCl_3$) δ 8.08-8.06 (br s, 3H), 5.66-5.59 (m, 1H), 5.00-4.94 (m, 1H), 4.82-4.75 (m, 1H), 3.45-3.37 (m, 1H), 3.32-3.20 (m, 1H). Mass spectrum API-TIS- *m/z* 182 (MH^+).

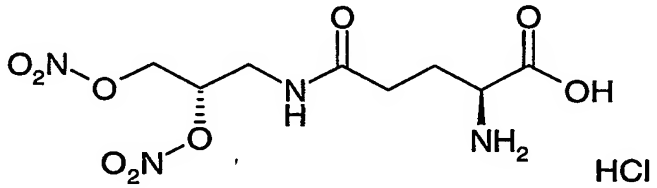
19b. tert-Butyl (2S)-4-{N-[(2S)-2,3-bis(nitrooxy)propyl]carbamoyl}-2-[(tert-butoxy)carbonylamino]butanoate



BOC-L-Glutamic acid alpha tert-butyl ester (1.3g, 4.3 mmol), the product of Example 19a (1.1 g, 4.6 mmol), and DMAP (523.1 mg, 4.3 mmol) were dissolved in CH_2Cl_2 (15 mL) and EDAC (991.0 mg, 5.2 mmol) were added. The mixture was stirred at room temperature overnight and then washed with water and brine. The

organics were collected, dried over $MgSO_4$, and the solvent removed under reduced pressure. Purification of the oil via column chromatography (2:1 hexanes/EtOAc) give the title compound (1.5 g, 73% yield) as a yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ 5.46-5.44 (m, 1H), 5.33-5.31 (m, 1H), 4.89-4.84 (m, 1H), 4.61-4.55 (m, 1H), 3.80-3.78 (m, 1H), 3.55-3.48 (m, 1H), 2.34-2.29 (m, 1H), 2.28-2.19 (m, 1H), 2.05 (br s, 2H), 1.47 (s, 9H), 1.45 (s, 9H). Mass spectrum API-TIS- *m/z* 467 (MH^+).

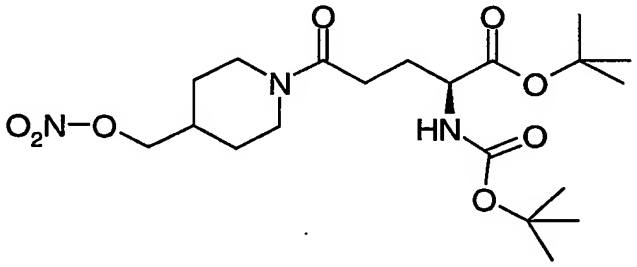
19c. (2S)-4-{N-[(2S)-2,3-Bis(nitrooxy)propyl]carbamoyl}-2-aminobutanoic acid, hydrochloride salt



The title compound will be prepared from the product of Example 19b using the procedure for Example 8c.

Example 20: (2S)-2-Amino-5-{4-[(nitrooxy)methyl]oiperidyl}-5-oxopentanoic acid, hydrochloride salt

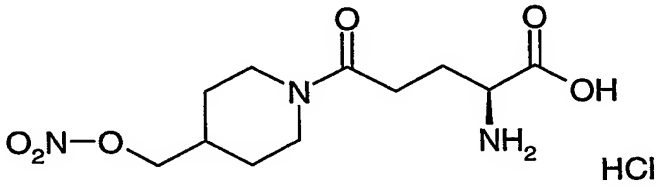
20a. tert-Butyl (2S)-2-[(tert-butoxy)carbonylamino]-5-{4-[(nitrooxy)methyl] piperidyl}-5-oxopentanoate



BOC-L-Glutamic acid alpha tert-butyl ester (1.2 g, 3.9 mmol), nitrooxy(4-piperidylmethyl)-nitric acid salt (prepared as described for US 2004/0024057, Example 19a) (1.0 g, 4.7 mmol), and DMAP (469.4 mg, 3.9 mmol) were dissolved in CH_2Cl_2 and EDAC (890.7 mg, 4.7 mmol) was added. The mixture was stirred at room temperature for 4.5 hours and washed with water and brine. The organics were separated, dried ($MgSO_4$), and the solvent removed under reduced pressure.

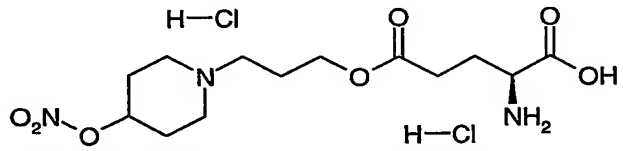
Purification of the resulting residue through a silica gel plug (1:1 hexanes/EtOAc) gave the title compound (1.4 g, 83% yield) as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.19-5.14 (m,1H), 4.65-4.62 (m, 1H), 4.33-4.29 (m, 2H), 4.21 (m, NH), 3.86-3.84 (m, 1H), 3.04-2.99 (m, 1H), 2.56-2.34 (m, 3H), 2.29-2.20 (m, 1H), 2.02-1.72 (m, 2H), 1.46 (s, 9H), 1.44 (s, 9H), 1.28-1.20 (m, 2H). Mass spectrum API-TIS- *m/z* 446 (MH^+).

20b. (2S)-2-amino-5-{4-[(nitrooxy)methyl]piperidyl}-5-oxopentanoic acid, hydrochloride salt

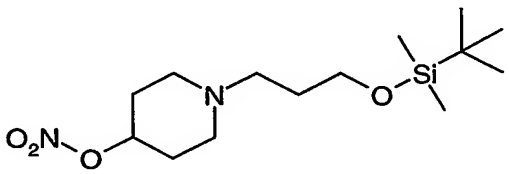


The title compound will be prepared from the product of Example 20a using the procedure for Example 8c.

Example 21: (2*S*)-2-amino-5-{3-[4-(nitrooxy)piperidin-1-yl]propoxy}-5-oxopentanoic acid dihydrochloride salt

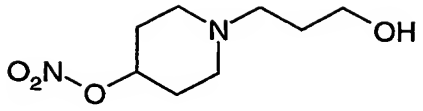


21a. Nitrooxy{1-[3-(1,1,2,2-tetramethyl-1-silapropoxy)propyl](4-piperidyl)}



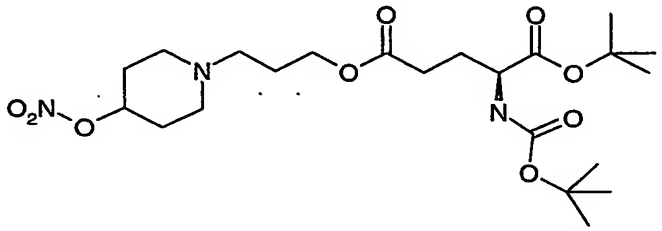
The title compound was prepared as colorless oil (2.76 g, 87%) from the product of Example 16a and 3-(bromopropoxy)-tert-butyldimethylsilane using the procedure for Example 17a. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.94 (m, J = 4.1 Hz, 1H), 3.63 (t, J = 6.2 Hz, 2H), 2.70-2.42 (m, 2H), 2.40 (t, J = 7.4 Hz, 2H), 2.29-2.24 (m, 2H), 2.03-1.97 (m, 2H), 1.81-1.77 (m, 2H), 1.69-1.62 (m, 2H), 0.87 (s, 9H), 0.04 (s, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 79.9, 61.1, 54.7, 50.4, 30.2, 29.2, 25.8, 18.2, -5.4. LRMS (APIMS) *m/z* 319 (MH^+).

21b. 3-[4-(Nitrooxy)piperidyl]propan-1-ol



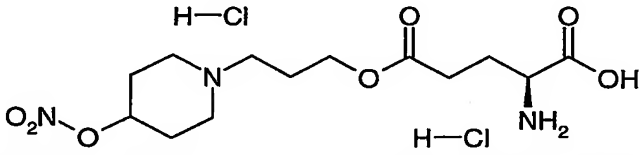
The title compound was prepared as colorless oil (1.24 g, 70% yield) from the product of Example 21a by following the procedure for Example 17b. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.98 (m, J = 3.9 Hz, 1H), 4.85-4.20 (br s, 1H), 3.77 (t, J = 5.3 Hz, 2H), 2.75 (br s, 2H), 2.60 (t, J = 5.9 Hz, 2H), 2.40 (m, 2H), 2.04-1.97 (m, 2H), 1.86-1.79 (m, 2H), 1.78-1.69 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 78.5, 63.8, 57.9, 49.9, 28.7, 26.9. LRMS (APIMS) *m/z* 205 (MH^+).

21c. tert-Butyl 3-[4-(nitrooxy)piperidyl]propyl (2S)-2-[(tert-butoxy)carbonylamino]pentane-1,5-dioate



The title compound was prepared as colorless oil (0.3 g, 21% yield) from the product of Example 21b following the procedure for Example 17c. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.13-5.10 (m, 1H), 5.00 (m, J = 3.89 Hz, 1H), 4.20-4.11 (m, 3H), 2.80-2.73 (m, 2H), 2.49-1.81 (m, 14H), 1.47 (s, 9H), 1.44 (s, 9H). LRMS (APIMS) *m/z* 490 (MH^+).

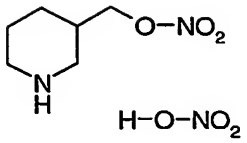
21d. (2*S*)-2-Amino-5-{3-[4-(nitrooxy)piperidin-1-yl]propoxy}-5-oxopentanoic acid dihydrochloride salt



The title compound will be prepared from the product of Example 21c using the procedure for Example 17c.

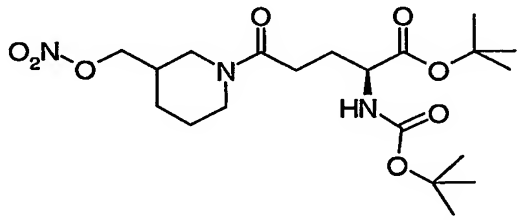
Example 22: (2S)-2-Amino-5-{3-[(nitrooxy)methyl]piperidyl}-5-oxopentanoic acid, hydrochloride salt

22a. Nitrooxy(3-piperidylmethyl), nitric acid salt



Piperidine-3-methanol (2.3 g, 20 mmol) was dissolved in ethyl acetate (60 mL) and the solution was cooled using an ice bath. To the solution, fuming nitric acid (1 mL) was added to generate *in situ* the nitrate salt. In a separate flask the nitrating reagent was prepared by mixing acetic anhydride (17 mL, 180 mmol) and fuming nitric acid (4.2 mL, 100 mmol) while cooling on an ice bath. The nitrating solution was then added slowly at 0 °C and the reaction mixture was stirred at 0 °C for 15 minutes, and then at room temperature for 1 hr. The solvent was removed under reduced pressure and the residue obtained was dried overnight under high vacuum to yield the title compound (4.27 g, 96% yield) as colorless thick oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.70 (br s, 1H), 8.4 (br s, 1H), 4.60-4.43 (m, 2H), 3.75-3.20 (m, 2H), 2.90-2.75 (m 2H), 2.30-2.05 (m, 1H), 1.85-1.72 (m, 2H), 1.70-1.55 (m, 1H), 1.40-1.35 (m, 1H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 74.9, 45.5, 43.9, 31.9, 24.8, 21.7; LRMS (APIMS) *m/z* 161 (M – HNO_3 + H)$^+$.

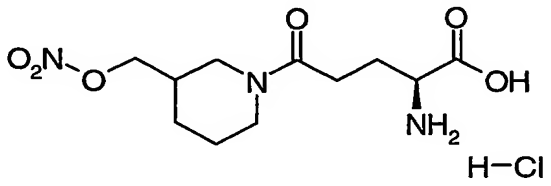
22b. tert-Butyl (2S)-2-[(tert-butoxy)carbonylamino]-5-{3-[(nitrooxy)methyl] piperidyl}-5-oxopentanoate



A mixture of BOC-L-glutamic acid alpha tert-butyl ester (3.15 g, 10 mmol) and the product of Example 22a (2.23 g, 10 mmol) in ethyl acetate (50 mL) and triethyl amine (1.4 mL, 10 mmol) was stirred at room temperature for 10 minutes. To this solution were added successively EDAC (1.92 g, 10 mmol) followed by DMAP (1.22 g, 10 mmol). The resulting solution was then stirred under nitrogen atmosphere at room temperature for 2 hours. The reaction mixture was then diluted with ethyl acetate and washed with water, aqueous $NaHCO_3$, brine, dried over sodium sulfate, filtered, and the solvent was evaporated at reduced pressure. The product was purified by column chromatography over silica gel using 40% ethyl acetate in hexane to give the title

compound (2.45 g, 57% yield) as colorless thick oil: ^{1}H NMR ($CDCl_3$) δ 5.20-5.10 (m, 1H), 4.40-4.00 (m, 4H), 3.85-3.75 (m, 1H), 3.2-1.8 (m, 11H), 1.43 (s, 9H), 1.41 (s, 9H); LRMS (APIMS) *m/z* 446 (MH^+), 908 ($M_2NH_4^+$).

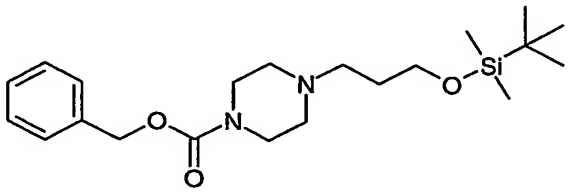
22c. (2S)-2-Amino-5-{3-[(nitrooxy)methyl]piperidyl}-5-oxopentanoic acid, hydrochloride salt



The product of Example 22a (1.1 g, 2.47 mmol) was dissolved in 4 M HCl in ethyl acetate (10 mL) and the resulting solution was stirred at room temperature for 8 hours. The solid that precipitated out was filtered off and washed with ethyl acetate and dried under high vacuum to give the title compound as a white solid (640 mg, 75% yield): mp 70-72 °C (with decomposation); ^{1}H NMR (d_6-DMSO) δ 14.0-13.8 (br s, 1H), 8.47 (s, 2H), 4.46-2.52 (m, 11H), 2.03-1.17 (m, 6H); LRMS (APIMS) *m/z* 290 (MH^+).

Example 23: (2S)-2-Amino-4-[(3-{4-[2,2-dimethyl-3-(nitrooxy)propanoyl] piperazinyl}propyl)oxycarbonyl]butanoic acid; bis hydrochloride salt

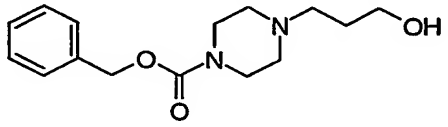
23a. Phenylmethyl 4-[3-(1,1,2,2-tetramethyl-1-silapropoxy)propyl] piperazinecarboxylate



Carbobenzyloxy piperazine (prepared as described in (Synthesis 759-763, 1997) (3.3 g, 15 mmol) and 3-(bromopropoxy)-tert-butyldimethylsilane (5.06 g, 20 mmol) were dissolved in anhydrous DMF (50 mL). To this mixture was added potassium carbonate (14 g, 0.1 mol) and stirred at room temperature for 2 days. It was then poured over ice-cold water, extracted with ethyl acetate. The combined extracts were

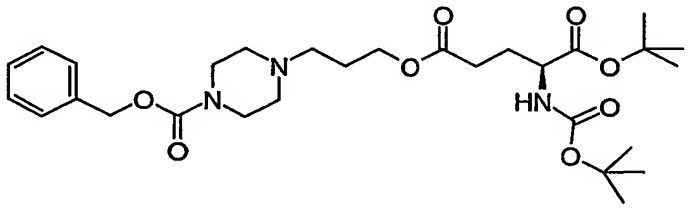
washed with water, dried, and solvent was evaporated at reduced pressure to give the crude product that was purified by column chromatography over silica gel using 5% methanol in dichloromethane to give the title compound (2.8 g, 48% yield) as colorless thick oil: ^{1}H NMR ($CDCl_3$) δ 7.35 (s, 5H), 5.11 (s, 2H), 3.72 (t, J = 6.6 Hz, 2H), 3.50 (t, J = 5.1 Hz, 4H), 2.42-2.38 (m, 6H), 1.72-1.61 (m, 2H), 0.87 (s, 9H), - 0.01 (s, 6H); LRMS (APIMS) *m/z* 393 (MH^+).

23b. Phenylmethyl 4-(3-hydroxypropyl)piperazinecarboxylate



The product of the Example 23a (2.7 g, 6.88 mmol) was dissolved in anhydrous THF (25 mL) and tetrabutyl ammonium fluoride (1 M in THF, 10 mL, 10 mmol) was added under nitrogen. The reaction mixture was stirred at room temperature overnight. The solvent THF was evaporated at reduced pressure, and the crude product was purified by column chromatography over silica gel using 5% methanol in dichloromethane to give the title compound as colorless thick oil: ^{1}H NMR ($CDCl_3$) δ 7.26 (s, 5H), 5.10 (s, 2H), 3.77 (t, J = 5.3 Hz, 2H), 3.51-3.48 (m, 4H), 3.28-3.15 (m, 1H, OH), 2.59 (t, J = 5.8 Hz, 2H), 2.55-2.45 (m, 4H), 1.77-1.65 (m, 2H); LRMS (APIMS) *m/z* 279 (MH^+), 557 (M_2H^+).

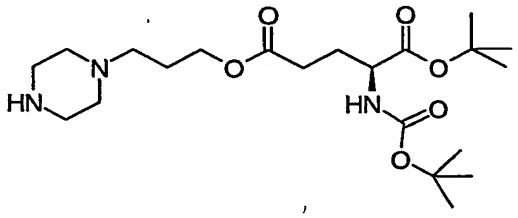
23c. tert-Butyl 3-{4-[benzyloxycarbonyl]piperazinyl}propyl (2S)-2-[(tert-butoxy)carbonylamino]pentane-1,5-dioate



To a mixture of BOC-L-glutamic acid alpha tert-butyl ester (1.57g, 5 mmol) and product of the Example 23b (1.39 g, 5 mmol) in dichloromethane (25 mL) were added successively EDAC (0.96 g, 5 mmol) followed by DMAP (0.61 g, 5 mmol) and the resulting solution was stirred under nitrogen atmosphere at room temperature overnight. The reaction mixture was then diluted with dichloromethane and washed with water, aqueous $NaHCO_3$, brine, dried over sodium sulfate, filtered, and the solvent was

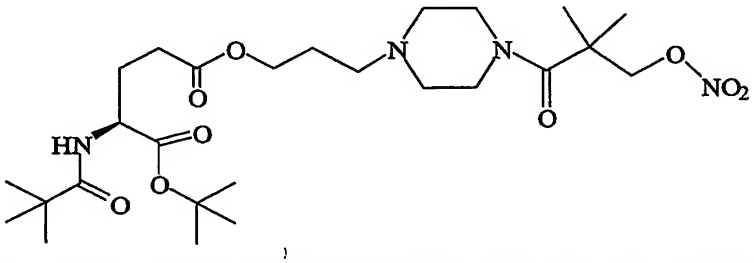
evaporated at reduced pressure. The product was purified by column chromatography over silica gel using 10% ethyl acetate in hexane to give the title compound (2.17 g, 77% yield) as colorless thick oil: ^{1}H NMR ($CDCl_3$) δ 7.60 (s, 5H), 5.11 (br s, 3H), 4.29-4.03 (m, 3H), 3.49-3.45 (m, 4H), 2.45-2.37 (m, 8H), 1.90-1.70 (m, 4H), 1.44 (s, 9H), 1.42 (s, 9H); LRMS (APIMS) *m/z* 564 (MH^+).

23d. tert-Butyl 3-piperazinylpropyl (2S)-2-[(tert-butoxy)carbonylamino]pentane-1,5-dioate



The product of the Example 23c (2.1 g) was dissolved in ethanol (75 mL) under nitrogen atmosphere; Pd/C (10%) was added. Hydrogenation was performed at 20 psi for 2 hours using par hydrogenation apparatus. The catalyst was removed by filtration and the filtrate was evaporated at reduced pressure to give the title compound as a colorless thick oil that was used as such in the next step without further purification.

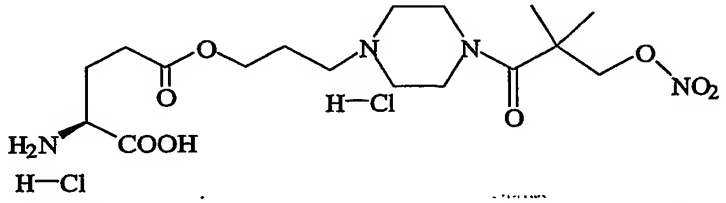
23e. tert-Butyl 3-{4-[2,2-dimethyl-3-(nitrooxy)propanoyl]piperazinyl}propyl (2S)-2-(2,2-dimethylpropanoylamino)pentane-1,5-dioate



A mixture of the product of Example 23d (160 mg, 0.4 mmol) and 2,2-dimethyl-3-(nitrooxy)propanoic acid (prepared as described in U.S. Patent No. 5,428,061, Example 3) (60 mg, 0.4 mmol) was dissolved in anhydrous dichloromethane (2 mL). To this solution were added successively 1-ethyl-3-(3-dimethylaminopropyl) carbamide hydrochloride (EDAC) (77 mg, 0.4 mmol) followed by dimethyl aminopyridine (DMAP, 49 mg, 0.4 mmol). The resulting solution was then stirred under nitrogen atmosphere at room temperature overnight. The reaction mixture was diluted with dichloromethane and washed with water, aqueous $NaHCO_3$, water, brine,

dried over sodium sulfate, filtered, and the solvent was evaporated at reduced pressure. The product was purified by column chromatography over silica gel using ethyl acetate to give the title compound (160 mg, 72% yield) as colorless thick oil: ^{1}H NMR ($CDCl_3$) δ 5.10 (br s, 1H), 4.52 (s, 2H), 4.16-4.00 (m, 3H), 3.67 (m, 4H), 2.40-2.27 (m, 8H), 2.20-2.10 (m, 1H), 1.90-1.70 (m, 3H), 1.42 (s, 9H), 1.40 (s, 9H), 1.32 (s, 6H); LRMS (APIMS) *m/z* 575 (MH^+).

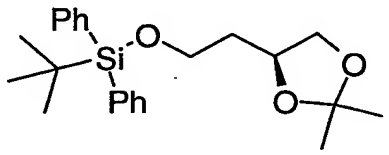
23f. (2S)-2-Amino-4-[(3-{4-[2,2-dimethyl-3-(nitrooxy)propanoyl] piperazinyl} propyl)oxycarbonyl]butanoic acid; dihydrochloride salt



The title compound will be prepared from the product of Example 23e using the procedure for Example 5c.

Example 24: 4-{[(3R)-3,4-Bis(nitrooxy)butyl]oxycarbonyl}(2S)-2-aminobutanoic acid, hydrochloride salt

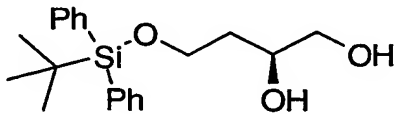
24a. 1-[2-((4S)-2,2-Dimethyl(1,3-dioxolan-4-yl))ethoxy]-2,2-dimethyl-1,1-diphenyl-1-silapropane



A solution of (4s)-(+)-4-(2-hydroxymethyl)-2,2-dimethyl 1,3-dioxolane (Aldrich, Milwaukee, US, 14.97 g, 102.4 mmol), tert-butyl dimethyl phenyl silyl chloride (30.91g, 112.54 mmol), triethylamine (15.8 mL, 113.4 mmol) and DMAP (1.08 g, 8.84 mmol) in CH_2Cl_2 (200 mL) was stirred at room temperature overnight. The reaction mixture was washed with 3N HCl, brine, dried over Na_2SO_4, filtered, concentrated and dried under vacuum. The product was separated by silica gel column chromatography eluting with EtOAc:hexane (gradient from 0% to 1:10, $Rf = 0.3$) to give the title compound as a sticky oil (27.37 g, 70% yield): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.70-7.60 (m, 4H), 7.40-7.30 (m, 6H), 4.27-4.23 (m, 1H), 4.10-4.00 (m, 1H), 3.80-3.70 (m, 2H), 3.60-3.55 (m, 1H), 1.90-1.70 (m, 2H), 1.38 (s, 3H), 1.35 (s, 3H),

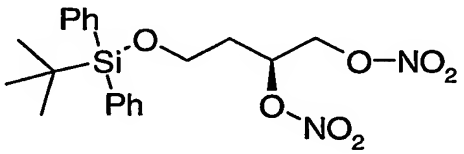
1.06 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 135.62, 135.5, 133.58, 133.56, 129.62, 129.60, 127.63, 108.28, 73.9, 69.8, 60.8, 36.4, 26.9, 26.8, 25.8, 19.1. Mass spectrum (API-TIS) *m/z* 385 (MH^+). Anal. Calcd for $C_{23}H_{32}O_3Si$: C, 71.83; H, 8.39. Found: C, 71.82; H, 8.45.

24b. (2S)-4-(2,2-Dimethyl-1,1-diphenyl-1-silapropoxy)butane-1,2-diol



The product of Example 24a (13.84 g, 36 mmol) was heated to 70-75 °C in a mixture of acetic acid (35 mL) and water (15 mL) for 45 minutes. The resulting clear solution was cooled to room temperature and evaporated to dryness under vacuum. The resulted material was dissolved in ethyl acetate (150 mL), washed with water, 5% $NaHCO_3$, and brine, dried over Na_2SO_4, filtered, concentrated and dried under vacuum. The crude product was treated with hexane to give the title compound as a white solid (6.94 g, 56 % yield): mp 70-72 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.70-7.65 (m, 4H), 7.50-7.20 (m, 6H), 4.04-4.00 (m, 1H), 3.90-3.80 (m, 2H), 3.70-3.50 (m, 2H), 3.37 (br, 1H), 2.24 (br, 1H), 1.90-1.60 (m, 2H), 1.06 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 135.48, 135.46, 132.9, 132.8, 129.8, 127.8, 71.5, 66.7, 62.5, 34.8, 26.8, 19.0. Mass spectrum (API-TIS) *m/z* 345 $(MH)^+$. Anal. Calcd for $C_{20}H_{28}O_3Si$: C, 69.73; H, 8.19. Found: C, 69.51; H, 8.46.

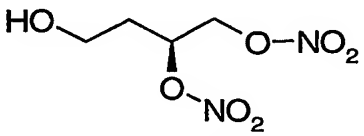
24c. [(2S)-4-(2,2-Dimethyl-1,1-diphenyl-1-silapropoxy)-2-(nitrooxy)butyl]nitrooxy



A solution of the product of Example 24b (15.13 g, 43.9 mmol) in EtOAc (150 mL) was added to an ice-cooled solution of fuming nitric acid (90%, 11 mL, 238 mmol) and acetic anhydride (55 mL). The reaction was stirred in an ice-bath for 10 minutes and then an additional 1.5 hours at room temperature. The reaction mixture was evaporated to dryness under vacuum at 40°C. The product was separated by silica gel column chromatography eluting with EtOAc:hexane (1:10, $Rf = 0.35$) to give the title compound as a clear oil (18.87 g, 99% yield): ^1H NMR (300 MHz, $CDCl_3$) δ 7.70-7.60

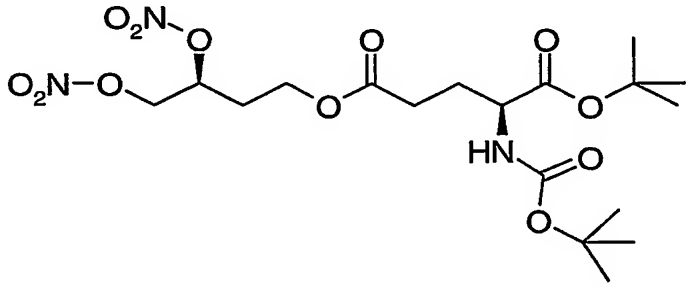
(m, 4H), 7.50-7.30 (m, 6H), 5.65-5.50 (m, 1H), 4.90-4.80 (m, 1H), 4.50-4.45 (m, 1H), 3.77 (t, J = 5.6 Hz, 2H), 1.95-1.89 (m, 2H), 1.06 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 135.42, 135.4, 132.9, 132.7, 130.0, 127.9, 76.6, 71.5, 58.8, 31.9, 26.7, 19.0. Mass spectrum (API-TIS) *m/z* 452 (MNH_4^+).

24d. (3S)-3,4-Bis(nitrooxy)butan-1-ol



A mixture of the product of Example 24c (5.38 g, 15.62 mmol) and KF (2.74 g, 47.1 mmol) in methanol (120 mL) was heated to reflux for 24 hours. The solvent was evaporated to dryness under reduced pressure. The product was separated by silica gel column chromatography eluting with EtOAc:hexane (gradient from 1:2 to 1:1, Rf = 0.25 in 1:1) to give the title compound as a clear oil (1.88 g, 61% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.60-5.50 (m, 1H), 4.90-4.80 (m, 1H), 4.60-4.50 (m, 1H), 3.85-3.7(m, 2H), 2.17 (s, 1H), 2.10-1.90 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 76.9, 71.5, 57.6, 31.6. Mass spectrum (API-TIS) *m/z* 214 (MNH_4^+).

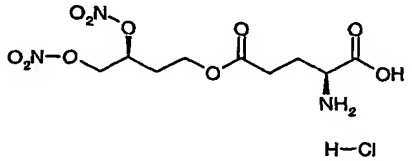
24e. (3S)-3,4-Bis(nitrooxy)butyl tert-butyl (2S)-2-[(tert-butoxy)carbonylamino] pentane-1,5-dioate



A solution of (4S)-4-[(tert-butyl)oxycarbonyl]-4-[(tert-butoxy)carbonylamino]-butanoic acid (3.11 g, 10.3 mmol), 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride (2.57 g, 13.4 mmol), N,N-dimethylaminopyridine (0.21 g, 1.7 mmol) and the product of Example 24d (1.85 g, 9.45 mmol) in CH_2Cl_2 (100 mL) was stirred at room temperature overnight. The reaction mixture was partitioned between 3N HCl (50 mL) and CH_2Cl_2 (50 mL x 2). The combined organic extracts were washed with water, 5% Na_2CO_3, 3N HCl, brine, dried over Na_2SO_4, filtered, concentrated and dried under vacuum. The product was separated by silica gel column chromatography eluting

with EtOAc:hexane (gradient from 1:3 to 1:2, R*f* = 0.25 in 1:2) to give the title compound as a clear oil (3.62 g, 73% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.50-5.40 (m, 1H), 5.15 (br. d, 1H), 4.90-4.80 (m, 1H), 4.60-4.50 (m, 1H), 4.30-4.10 (m, 3H), 2.50-2.30 (m, 2H), 2.20-2.00 (m, 3H), 2.00-1.80 (m, 1H), 1.47 (s, 9H), 1.44 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3, 171.1, 155.3, 82.1, 79.6, 76.3, 71.0, 59.4, 53.0, 29.9, 28.5, 28.2, 27.9, 27.8. Mass spectrum (API-TIS) *m/z* 482 $(MH)^+$.

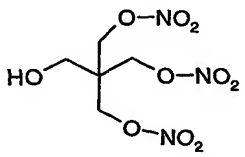
24f. 4-{[(3R)-3,4-Bis(nitrooxy)butyl]oxycarbonyl}(2S)-2-aminobutanoic acid, hydrochloride salt



The title compound will be prepared from the product of Example 24e using the procedure for Example 8c.

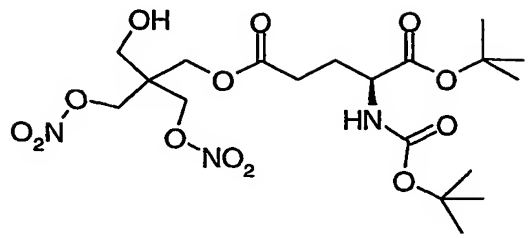
Example 25: (2S)-2-Amino-4-({2,2-bis[(nitrooxy)methyl]-3-hydroxypropyl} oxycarbonyl)butanoic acid, hydrochloride salt

25a. 2,2-Bis[(nitrooxy)methyl]-3-(nitrooxy)propan-1-ol

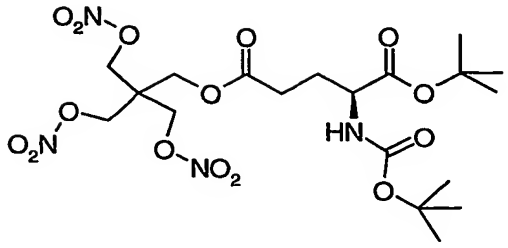


The title compound was prepared using the procedure described in WO 00/51978, Example 11c. A mixture tri- and di-nitrate were obtained and were used in the next step without further purification. Di-nitrate: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.49 (s, 4H), 3.68 (s, 4H).

25b. tert-Butyl 2,2-bis[(nitrooxy)methyl]-3-hydroxypropyl (2S)-2-[(tert-butoxy)carbonylamino]pentane-1,5-dioate and tert-Butyl 2,2-bis[(nitrooxy)methyl]-3-(nitrooxy)propyl (2S)-2-[(tert-butoxy)carbonylamino]pentane-1,5-dioate

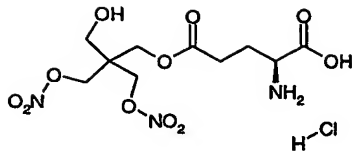


and



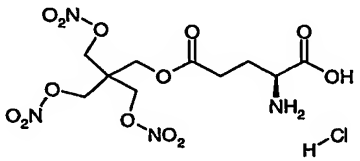
A solution of the product of Example 25a (3.07 g), (4S)-4-[(tert-butyl)oxycarbonyl]-4-[(tert-butoxy)carbonylamino]-butanoic acid (3.6 g, 11.9 mmol), triethylamine (1.6 mL, 11.5 mmol), 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride (2.98 g, 15.5 mmol), and N,N-dimethylaminopyridine (0.2 g, 1.7 mmol) in CH_2Cl_2 (60 mL) was stirred at room temperature overnight. The reaction mixture was partitioned between 3N HCl (50 mL) and CH_2Cl_2 (50 mL x 2). The combined organic extracts were washed with water, 5% Na_2CO_3, 3N HCl, brine, dried over Na_2SO_4, filtered, concentrated and dried under vacuum. The product was separated by silica gel column chromatography eluting with EtOAc:hexane (1:3) to give the trinitrate ($Rf = 0.25$) as a clear oil (2.83 g, 45% yield) and the dinitrate ($Rf = 0.1$) as a clear oil (0.93 g, 16% yield). Dinitrate compound: tert-butyl 2,2-bis[(nitrooxy)methyl]-3-hydroxypropyl (2S)-2-[(tert-butoxy)carbonylamino]pentane-1,5-dioate: ^{1}H NMR (300 MHz, DMSO-d6, 350°K) δ 6.40 (br, 1H), 4.63 (s, 4H), 4.13 (s, 2H), 3.95-3.8 (m, 1H), 3.52 (s, 2H), 2.45-2.35 (m, 2H), 2.00-1.80 (m, 2H), 1.42 (s, 9H), 1.39 (s, 9H). ^{13}C NMR (300 MHz, DMSO-d6, 350°K) δ 171.2, 170.5, 154.7, 80.2, 77.9, 71.5, 62.1, 59.5, 53.5, 43.1, 29.6, 27.6, 27.2, 25.8. Mass spectrum (API-TIS) *m/z* 512 $(MH)^+$. Trinitrate compound: tert-butyl 2,2-bis[(nitrooxy)methyl]-3-(nitrooxy)propyl (2S)-2-[(tert-butoxy)carbonylamino]pentane-1,5-dioate: ^{1}H NMR (300 MHz, DMSO-d6, 350°K) δ 6.40 (br, 1H), 4.72 (s, 6H), 4.21 (s, 2H), 3.95-3.85 (m, 1H), 2.45-2.35 (m, 2H), 2.0-1.85 (m, 2H), 1.42 (s, 9H), 1.39 (s, 9H). ^{13}C NMR (300 MHz, DMSO-d6, 350°K) δ 171.0, 170.4, 154.7, 80.3, 78.0, 70.5, 61.3, 53.4, 41.8, 29.5, 27.6, 27.2, 25.8. Mass spectrum (API-TIS) *m/z* 557 (MH^+).

25c. (2S)-2-Amino-4-({2,2-bis[(nitrooxy)methyl]-3-hydroxypropyl} oxycarbonyl)butanoic acid, hydrochloride salt



The title compound will be prepared from the dinitrate of Example 25b using procedure for Example 8c.

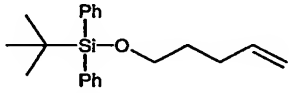
Example 26: (2S)-2-Amino-4-({2,2-bis[(nitrooxy)methyl]-3-(nitrooxy)propyl}oxycarbonyl)butanoic acid, hydrochloride salt



The title compound will be prepared from the trinitrate of Example 25b using procedure for Example 8c.

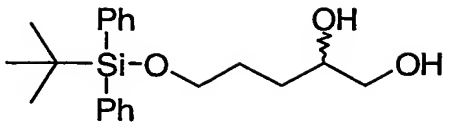
Example 27: (2S)-2-Amino-4-{[4,5-bis(nitrooxy)pentyl]oxycarbonyl}butanoic acid, hydrochloride salt

27a. 2,2-Dimethyl-1-pent-4-enyloxy-1,1-diphenyl-1-silapropane



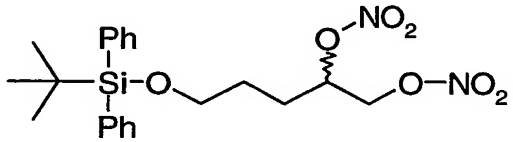
To a solution of 4-pentene-1-ol (Lancaster Synthesis, 8.76 g, 101.76 mmol), triethylamine (12.05 g, 119.06 mmol) and 4-dimethylaminopyridine (0.623 g, 5.09 mmol) in dichloromethane (200 mL) at 0 °C was added tert-butylchlorodiphenylsilane (Acros Organics, 29.37 g, 106.85 mmol) dropwise with stirring over 20 minutes. The reaction mixture was warmed to room temperature, and stirred overnight. The reaction mixture was partitioned between water and dichloromethane. The organic layer was washed with 1N HCl, water (2X) saturated sodium bicarbonate solution, brine, and dried over magnesium sulfate. The solvent was removed *in vacuo* to obtain the title compound (33.03 g, 100% yield) as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73-7.70 (m, 4H), 7.47-7.42 (m, 6H), 5.84 (m, 1H), 5.08-4.96 (m, 2H), 3.72 (t, J = 7.3 Hz, 2H), 2.23-2.14 (m, 2H), 1.74-1.66 (m, 2H), 1.09 (s, 9H); MS (API-TIS) *m/z* 325 (MH^+), 342 (MNH_4^+).

27b. 5-(2,2-Dimethyl-1,1-diphenyl-1-silapropoxy)pentane-1,2-diol



To the product of Example 27a (33.03 g, 101.76 mmol) in 350 mL of acetone at room temperature was added osmium tetroxide (Aldrich, 4% solution in water, 1.02 mmol, 6.47 mL). After 10 minutes, N-methylmorpholine-N-oxide (50% in water, 254.4 mmol, 29.8 g, 52.7 mL) was added, and the reaction mixture was stirred overnight at room temperature. Saturated sodium thiosulfate solution (200 mL) was added to the reaction mixture, and it was partitioned into ethyl acetate. The aqueous layer was back-extracted with ethyl acetate, and the combined organic layers were washed with 1N HCl until the extract was acidic, water (2X), saturated sodium bicarbonate solution, brine, and dried over magnesium sulfate. The solvent was removed *in vacuo* to give the title compound (36.5 g, 100% yield) as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68-7.65 (m, 4H), 7.44-7.39 (m, 6H), 3.75-3.61 (m, 2H), 3.70 (t, J = 7.3 Hz, 2H), 3.49-3.41 (m, 1H), 3.00 (m, 1H), 2.09 (m, 1H), 1.74-1.66 (m, 2H), 1.62-1.53 (m, 2H), 1.05 (s, 9H); MS (API-TIS) *m/z* 359 (MH^+), 376 (MNH_4^+), 734 ($2MNH_4^+$).

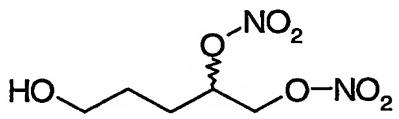
27c. [5-(2,2-Dimethyl-1,1-diphenyl-1-silapropoxy)-2-(nitrooxy)pentyl]nitrooxy



To acetic anhydride (651.26 mmol, 60 mL), cooled to 0 °C was added fuming nitric acid (Acros Organics, 407.04 mmol, 20 mL) dropwise via an addition funnel. The resulting solution was warmed to room temperature for 45 minutes. To the product of Example 27b (36.5 g, 101.76 mmol) in 400 mL of ethyl acetate at 0 °C was added the nitric acid/acetic anhydride solution via addition funnel and then stirred overnight at 0 °C. The reaction mixture was basified with saturated sodium carbonate, water, and solid potassium carbonate to pH ~ 8-9. The layers were separated, and the aqueous layer was washed with ethyl acetate. The combined organic layers were washed with water, brine, and dried over magnesium sulfate. The solvent was removed *in vacuo* to give the title compound (45.6 g, 100% yield) as a pale yellow oil: ^{1}H NMR (300 MHz,

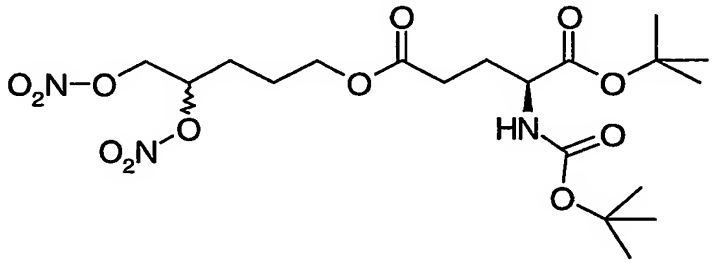
$CDCl_3$) δ 7.65-7.63 (m, 4H), 7.44-7.39 (m, 6H), 5.31 (ddd, *J* = 3.0, 6.6, 12.9 Hz, 1H), 4.71 (dd, *J* = 3.0, 12.9 Hz, 1H), 4.45 (dd, *J* = 6.6, 12.9 Hz, 1H), 3.70 (t, *J* = 6.0 Hz, 2H), 1.88-1.81 (m, 2H), 1.69-1.61 (m, 2H), 1.05 (s, 9H); MS (API-TIS) *m/z* 466 (MNH_4^+), 914 ($2MNH_4^+$).

27d. 4,5-Bis(nitrooxy)pentan-1-ol



To the product of Example 27c (45.6 g, 101.76 mmol) in acetonitrile (400 mL) in a polypropylene bottle at room temperature was added hydrofluoric acid (48% in water, 5.23 mol, 189 mL) via a polypropylene pipette. After 5 hours, TLC showed the reaction to be complete. The acid was quenched with sodium carbonate (solid and solution) to pH ~ 8-9. The liquid layer was poured into a separatory funnel. The semisolid residue in the bottle was rinsed with hexane, and the hexane wash was used to extract the acetonitrile in the separatory funnel. The acetonitrile layer was washed again with hexane, separated, and concentrated via rotory evaporation. The residue was redissolved in ethyl acetate, washed with saturated sodium carbonate, water, brine, and dried over magnesium sulfate. The solvent was removed *in vacuo* to give a pale yellow oil. This material was purified via column chromatography using silica gel, eluting with 50% ether/hexane to 100% ether to give the title compound (19.0 g, 89% yield) as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.38 (ddd, *J* = 3.0, 6.5, 12.9 Hz, 1H), 4.78 (dd, *J* = 3.0, 12.9 Hz, 1H), 4.50 (dd, *J* = 6.5, 12.9 Hz, 1H), 3.72 (t, *J* = 6.0, 2H), 1.92-1.84 (m, 2H), 1.79-1.66 (m, 2H), 1.57 (s, 1H); MS (API-TIS) *m/z* 228 (MNH_4^+), 438 ($2MNH_4^+$).

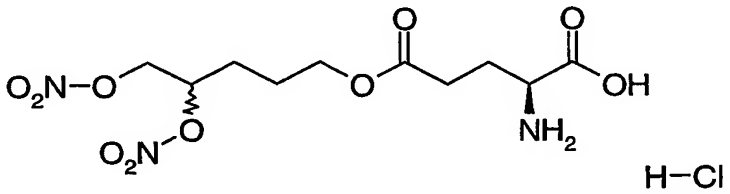
27e. tert-Butyl 4,5-bis(nitrooxy)pentyl (2S)-2-[(tert-butoxy)carbonylamino]pentane-1,5-dioate



A solution of the product of Example 27d (1.94 g, 9.24 mmol), (4S)-4-[(tert-

butyl)oxycarbonyl]-4-[(tert-butoxy)carbonylamino]-butanoic acid (3.05 g, 10.1 mmol), triethylamine (1.6 mL, 11.5 mmol), 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride (2.48 g, 12.9 mmol), and N,N-dimethylaminopyridine (0.21g, 1.7 mmol) in CH_2Cl_2 (60 mL) was stirred at room temperature overnight. The reaction mixture was partitioned between 3N HCl (50 mL) and CH_2Cl_2 (50 mL x 2). The combined organic extracts were washed with water, 5% Na_2CO_3, 3N HCl, brine, dried over Na_2SO_4, filtered, concentrated and dried under vacuum. The product was separated by silica gel column chromatography eluting with EtOAc:hexane (1:3, R*f* = 0.2) to give the title compound as a clear sticky oil (3.84 g, 77% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.50-5.30 (m, 1H), 5.25 (br. d, 1H), 4.85-4.75 (m, 1H), 4.60-4.50 (m, 1H), 4.30-4.00 (m, 3H), 2.50-2.40 (m, 2H), 2.30-2.00 (m, 1H), 2.00-1.70 (m, 5H), 1.47 (s, 9H), 1.44 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4, 171.0, 155.1, 81.7, 79.3, 78.6, 71.0, 63.1, 53.0, 29.8, 27.9, 27.6, 25.72, 25.69, 23.9. Mass spectrum (API-TIS) *m/z* 496 (MH^+).

27f. (2S)-2-Amino-4-{[4,5-bis(nitrooxy)pentyl]oxycarbonyl}butanoic acid, hydrochloride salt

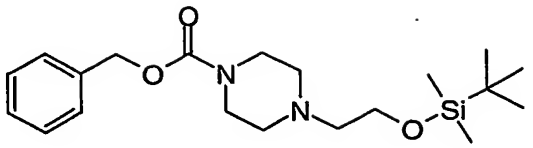


A solution of Example 27e (3.84 g, 7.8 mmol) in ethyl acetate (50 mL) was treated with HCl/ethyl acetate (10.59 g/50 mL, 290 mmol) and stirred at room temperature overnight. Hexane (150 mL) was added to the crude mixture and the resulted white solid was filtered, washed with Et_2O (50 mL) and dried under vacuum to give the title compound as a white sticky solid (2.12 g, 73% yield): mp 90-94 °C. ^{1}H NMR (300 MHz, CD_3OD) δ 5.50-5.45 (m, 1H), 5.00-4.90 (m, 1H), 4.70-4.60 (m, 1H), 4.30-4.10 (m, 2H), 4.10-4.00 (m, 1H), 2.70-2.60 (m, 2H), 2.30-2.10 (m, 2H), 1.9-1.8 (m, 4H). ^{13}C NMR (75 MHz, CD_3OD) δ 173.7, 171.4, 80.8, 72.9, 65.2, 53.1, 30.5, 26.8, 26.6, 25.2. Mass spectrum (API-TIS) *m/z* 340 ($M\text{-}Cl^+$), 368 ($MNH_4\text{-}Cl^+$).

Example 28: (2S)-2-Amino-4-[(2-{4-[2,2-dimethyl-3-(nitrooxy)propanoyl] piperazinyl}ethyl)oxycarbonyl]butanoic acid; bis hydrochloride salt

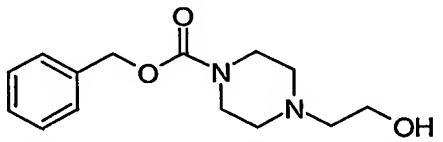
28a. Phenylmethyl 4-[2-(1,1,2,2-tetramethyl-1-silapropoxy)ethyl]

piperazinecarboxylate



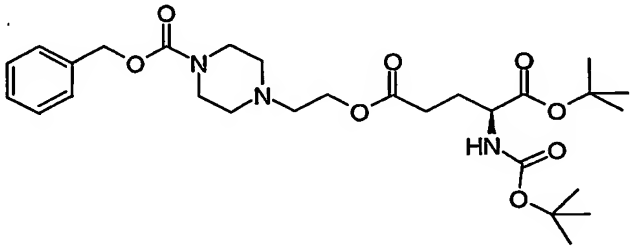
The title compound was prepared as a colorless thick oil (38% yield) from carbobenzyloxy piperazine (prepared as described in (Synthesis 759-763, 1997) and 2-(bromoethoxy)-tert-butyldimethylsilane using the procedure for Example 23a. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.29 (s, 5H), 5.36 (s, 2H), 3.73 (t, J = 6.1 Hz, 2H), 3.49 (t, J = 4.9 Hz, 2H), 2.53-2.47 (m, 8H), 0.88 (s, 9H), - 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 155.1, 137.6, 128.4 (2 x C), 127.9, 127.8 (2 x C), 77.2, 67.0, 61.2 (2 x C), 60.4 (2 x C), 53.4, 43.7, 25.8 (3 x C, t-Bu), 18.2 (2 x C); LRMS (APIMS) *m/z* 379 (MH^+).

28b. Phenylmethyl 4-(2-hydroxyethyl)piperazinecarboxylate



The product of Example 28a was reacted with TBAF following the procedure for Example 23b. The title compound was obtained in quantitative yield as a colorless thick oil: ^{1}H NMR ($CDCl_3$) δ 7.32 (s, 5H), 5.10 (s, 2H), 3.62 (t, J = 5.3 Hz, 2H), 3.51-3.40 (m, 4H), 3.0 (br s, 1H, OH), 2.53 (t, J = 5.5 Hz, 2H), 2.50-2.40 (m, 4H); LRMS (APIMS) *m/z* 265 (MH^+), 529 (2M + 1).

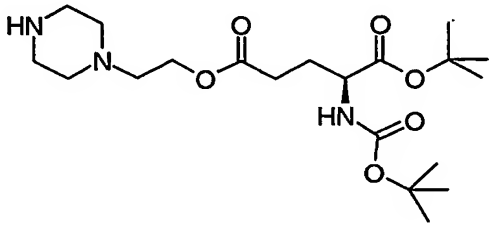
28c. tert-Butyl 2-{4-[benzyloxycarbonyl]piperazinyl}ethyl (2S)-2-[(tert-butoxy)carbonylamino]pentane-1,5-dioate



The product of Example 28b was coupled with BOC-L-glutamic acid alpha tert-butyl ester following the procedure for Example 23c. The title compound was obtained in 68% yield as a colorless thick oil: ^{1}H NMR ($CDCl_3$) δ 7.60 (s, 5H), 5.28 (m, 1H),

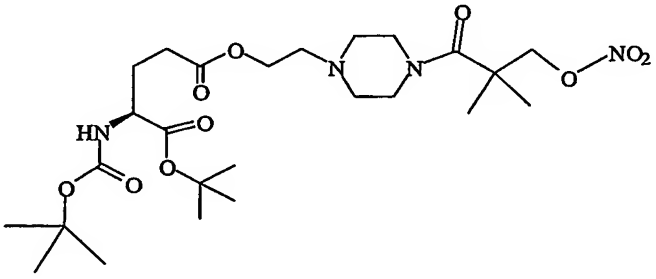
5.11 (s, 2H), 4.29-4.10 (m, 3H), 3.50-3.45 (m, 4H), 2.45-2.35 (m, 8H), 1.9-1.7 (m, 2H), 1.44 (s, 9H), 1.42 (s, 9H); LRMS (APIMS) *m/z* 550 (MH^+).

28d. tert-Butyl 2-piperazinylethyl (2S)-2-[(tert-butoxy)carbonylamino]pentane-1,5-dioate



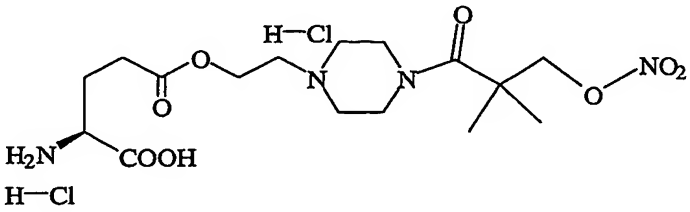
The product of Example 28c was hydrogenated following the procedure for Example 23d. The title compound was obtained in quantitative yield as colorless thick oil: ^1H NMR ($CDCl_3$) δ 5.25 (m, 1H), 4.29-4.10 (m, 3H), 2.95-2.80 (m, 4H), 2.65-2.35 (m, 8H), 2.20-2.05 (m, 1H), 1.80-1.70 (m, 1H), 1.44 (s, 9H), 1.42 (s, 9H); LRMS (APIMS) *m/z* 416 (MH^+).

28e. tert-Butyl 2-{4-[2,2-dimethyl-3-(nitrooxy)propanoyl]piperazinyl}ethyl (2S)-2-[(tert-butoxy)carbonylamino]pentane-1,5-dioate



The product of the Example 28d will be treated with carbobenzyloxy piperazine using the procedure for Example 23e to give the title compound.

28f. (2S)-2-Amino-4-[(2-{4-[2,2-dimethyl-3-(nitrooxy)propanoyl]piperazinyl} ethyl)oxycarbonyl]butanoic acid dihydrochloride salt



The title compound will be prepared from the product of Example 28e using the procedure for Example 5c.

The disclosure of each patent, patent application and publication cited or described in the present specification is hereby incorporated by reference herein in its entirety.

Although the invention has been set forth in detail, one skilled in the art will appreciate that numerous changes and modifications can be made to the invention, and that such changes and modifications can be made without departing from the spirit and scope of the invention.